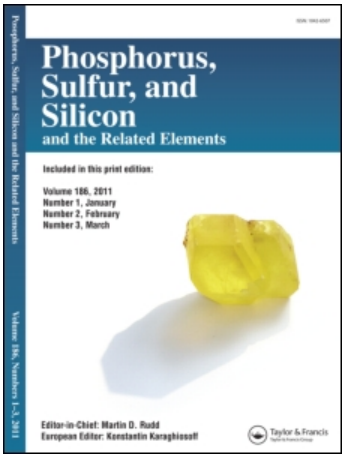

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Synthesis and Antimicrobial Evaluation of Some New 1,5-Benzothiazepine Derivatives and Their Ribofuranosides

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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NEW 1,5-BENZOTHIAZEPINE DERIVATIVES AND THEIR RIBOFURANOSIDES

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(±)-cis-*2(4-Methoxyphenyl)-3-hydroxy/methoxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5-benzothiazepin-4[5H/5-chloroacetyl/5-(4′-methylpiperazino-1′)acetyl]-ones have been synthesized by the condensation of 2-amino-3,5-dichloro/3-chloro benzenethiol with methyl-(±)*-trans-*3(4-methoxyphenyl)glycidate in xylene. Ribofuranosides viz (±)*-cis-*2(4-methoxyphenyl)-3-methoxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5-benzothiazepine-4-[5-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-ones have been synthesized by the treatment of 3-methoxy derivatives of 1,5-benzothiazepines with sugar viz β-D-ribofuranose-1-acetate-2,3,5-tribenzoate in toluene at vacuo. Synthesized compounds have been characterized by elemental analysis, IR, ^{1}H NMR spectral studies and screened for their antimicrobial activity.*

Keywords: 1,5-benzothiazepines; antimicrobial activity; ribofuranosides; spectral studies

INTRODUCTION

Perusal of literature, on pharamacological studies reported for 1,5-benzothiazepines class of compounds reveals that these compounds have immense chemotherapeutic importance of antihypertensive,[1] cardiovascular,[2] antiasthemic,[3,4] anticancer,[5] antipnotic,[6] antiherpe,[7] and antibacterial.[8] On the basis of structural activity relationship, it is significant to note that development of 1,5-benzothiazepines, like clobazam[9] and trifluorobazam[10] as CNS and CVS active agents. Krapcho[11] patented 1,5-benzothiazepine derivatives, as CNS depressant and antispasmodic.

Literature surveys have revealed that the condensation of silylated heterocyclic bases with sugar is a convenient synthetic method

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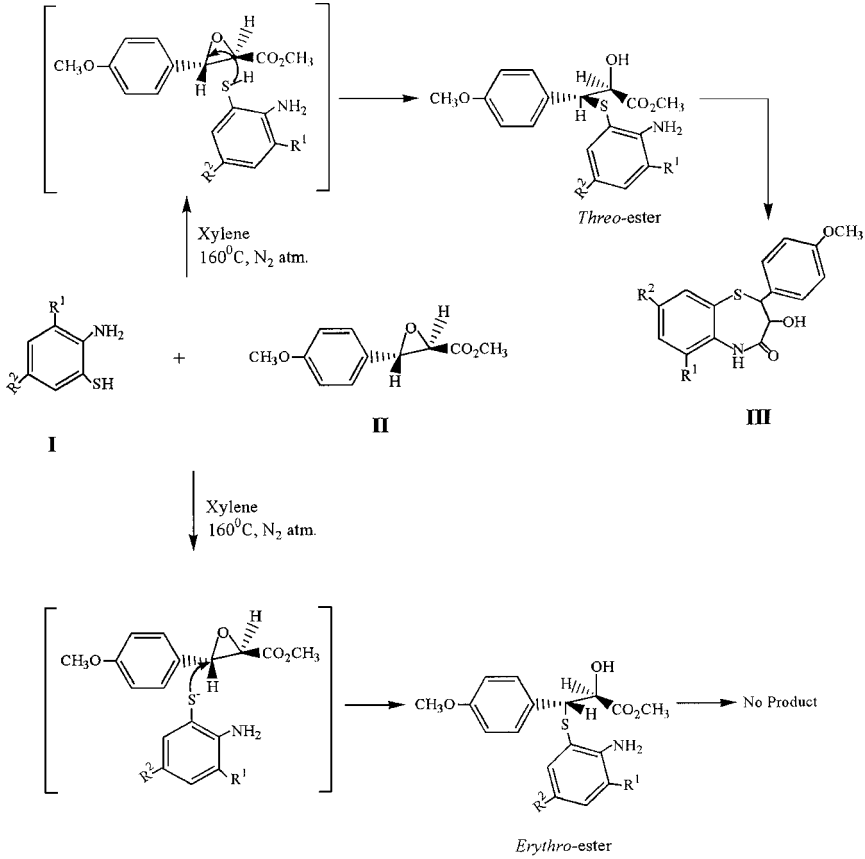
for the synthesis of nucleosides.[12] It has also been observed that in the synthesis of nucleosides, the intermediate species i.e., silylated heterocyclic bases are obtained only from the bases having —NHCO or —NHCS moieties. The manifold applications of this nuclei and our interest in this area[13] attracted our attention to synthesize some new 1,5-benzothiazepines and their ribofuranosides. These derivatives have been screened for their antimicrobial activities with the view to search some new medicinally important drugs.

RESULTS AND DISCUSSION

Synthesis of (±)-*cis*-2(4-methoxyphenyl)-3-hydroxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5-benzothiazepin-4[5*H*]-ones **III** were prepared by the condensation of 3,5-dichloro/3-chloro-benzenethiols **I** with methyl-(±)-*trans*-3(4-methoxyphenyl)glycidate **II** in xylene at 160°C, for 20–25 h, under nitrogen atmosphere in 80–82% yield. In our method no *trans* product was isolated. The *cis*-product of compound **III** appears to form via *threo*-ester, which upon cyclization yield the desired compound **III**. The *trans*-isomer of compound **III** was not obtained, as it should form via *erythro*-ester. These observations are in agreement with earlier report,[14] which observed that *erythro*-ester is formed only in the presence of a catalyst (Scheme 1).

(±)-*cis*-2(4-Methoxyphenyl)-3-methoxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5-benzothiazepin-4[5*H*]-ones **IV** were prepared by the treatment of compound **III** with dimethyl sulphate. (±)-*cis*-2(4-Methoxyphenyl)-3-methoxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5-benzothiazepin-4[5-chloroacetyl]-ones **V** were synthesized by the treatment of compound **IV** with chloroacetyl chloride. (±)-*cis*-2(4-Methoxyphenyl)-3-methoxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5-benzothiazepin-4[5-(4′-methylpiperazino-1′)acetyl]-ones, **VI** were synthesized by the condensation of compound **V**, with N-methylpiperazine.

(±)-*cis*-2(4-Methoxyphenyl)-3-methoxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5-benzothiazepin-4[5*H*]-ones **IV**, on treatment with hexamethyldisilazane in presence of ammonium sulphate produced corresponding trimethylsilyl derivatives **VII**, which, when stirred with sugar viz β-D-ribofuranose-1-acetate-2,3,5-tribenzoate **VIII** in toluene in vacuo at 155–160°C, afford ribofuranosides viz (±)-*cis*-2(4-methoxyphenyl)-3-methoxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5-benzothiazepin-4[5-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)]-ones **IX** (Scheme 2).



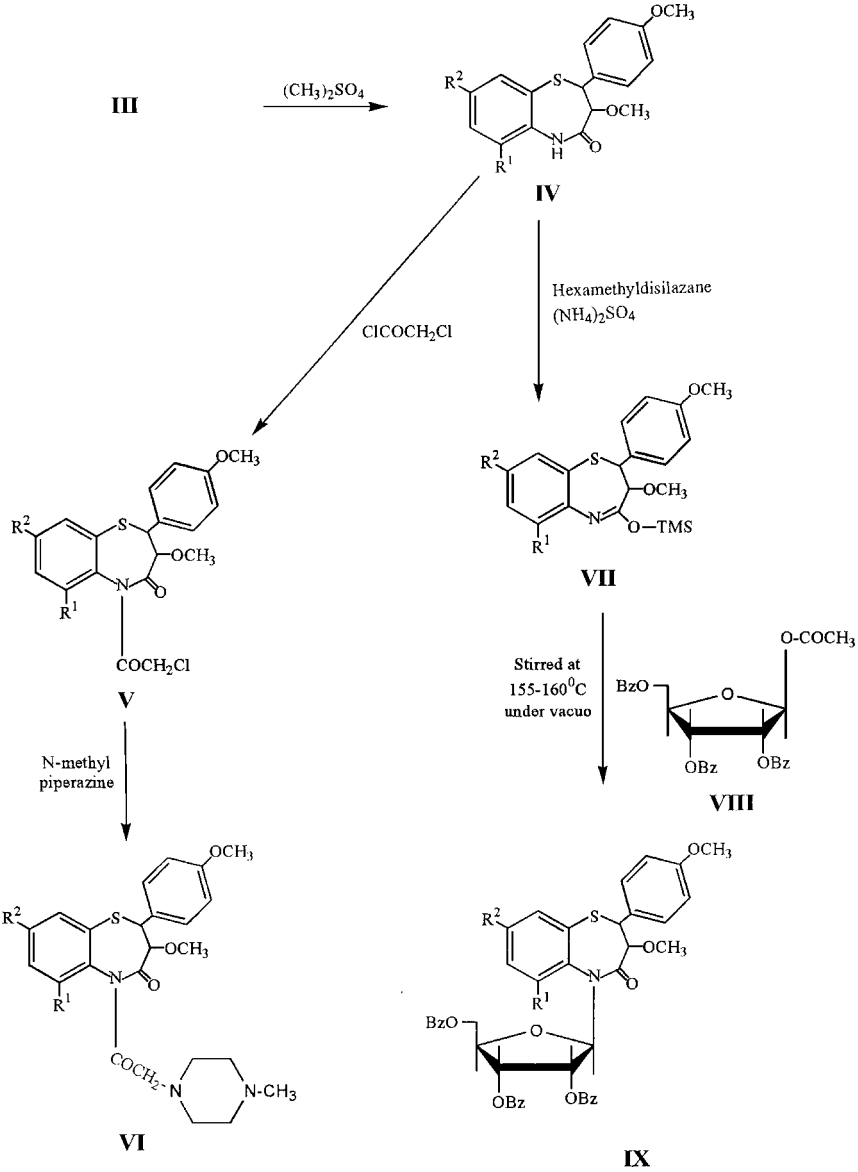
SCHEME 1

SPECTRAL DATA

The structures of all the synthesized compounds were confirmed by their elemental analysis, IR and ^{1}H NMR spectral data (Table I).

IR

In the compounds **III**, a broad band in the region 3550–3110 cm^{-1} was obtained due to >NH and —OH stretching vibrations. Compounds **IV** showed a less broad band in the region 3460–3130 cm^{-1} due to presence only >NH group. This band was absent in compounds **V**, **VI**, and **IX**. The >NH bending vibrations were observed as a sharp, medium to strong band, at 1550–1500 cm^{-1} in compounds **III** and **IV**. The C—S—C



SCHEME 2

linkage of seven-membered ring caused a weak and sharp absorption band at 685–630 cm^{-1}. The >C=O group was observed as a sharp and strong band in the region 1730–1630 cm^{-1} in all the synthesized compounds. In compounds **IV**, >NH band was completely vanished

TABLE I IR and ^{1}HNMR Spectral Data of 1,5-Benzothiazepines and Their Ribofuranosides

Comp. No.[a]	R^1	R^2	m.p. (°C)	Yield (%)	IR (KBr : ν_{max} cm^{-1})	^{1}HNMR (δ, ppm from TMS) $CDCl_3$/DMSO-d_6
IIIa	Cl	Cl	195	82	3490–3350 (NH/OH), 1580 (C═C, aro), 2910 (CH, ali), 3050 (CH, aro), 1650 (C═O) 1210–1050 (C—O—C), 680 (C—S—C),	8.30 (s, >NH), 6.82–7.32 (m, 6H, Ar—H), 3.75 (s, —OCH_3), 9.20 (s, OH) 2.40–3.80 (d, J = 8 Hz, C_2—H, C_3—H)
IIIb	Cl	H	185	80	3460–3350 (NH/OH), 1560 (C═C, aro), 2935 (CH, ali) 3040 (CH, aro), 1640 (C═O), 1210–1070 (C—O—C), 660 (C—S—C)	8.25 (s, >NH), 6.80–7.90 (m, 7H, Ar—H), 3.60 (s, OCH_3), 9.20 (s, OH), 2.40–3.76 (d, J = 8 Hz, C_2—H, C_3—H)
IVa	Cl	Cl	210	75	3370–3230(NH), 1590 (C═C, aro), 2930 (CH, ali), 3060 (CH, aro), 1650 (C═O), 1250–1030 (C—O—C), 650 (C—S—C)	8.30 (s, NH), 6.50–8.10 (m, 6H, Ar—H), 3.72 (s, Ar—OCH_3), 3.61 (d, benzothiaza—OCH_3), 2.41–3.76 (d, J-8 Hz, C_2—H, C_3—H)
IVb	Cl	H	230	67	3450 (NH), 1565 (C═C, aro), 2920 (CH, ali), 3030 (CH, aro), 1620 (C═O), 1200–1050 (C—O—C), 650 (C—S—C)	8.20 (s, NH), 7.20–8.00 (m, 7H, Ar—H), 3.80 (s, Ar—OCH_3), 3.62 (d, benzothiaza—OCH_3), 2.42–3.72 (d, J = 8 Hz, C_3—H, C_3—H)
Va	Cl	Cl	140	70	1590 (C═C, aro), 2940 (CH, ali), 3020 (CH, aro) 1665 (C═O), 1230–1070 (C—O—C), 665 (C—S—C)	6.87–8.70 (m, 6H, Ar—H), 3.90 (s, Ar—OCH_3), 3.65 (d, benzothiaza—OCH_3), 4.10 (s, $COCH_2Cl$), 2.41–3.77 (d, J = 8 Hz, C_2—H, C_3—H)
Vb	Cl	H	160	72	1540 (C═C, aro), 2905 (CH, ali), 3025 (CH, aro), 1620 (C═O), 1210–1090 (C—O—C), 680 (C—S—C)	6.80–8.20 (m, 7H, Ar—H), 3.95 (s, Ar—OCH_3), 3.64 (d, benzothiaza—OCH_3), 4.20 (s, $COCH_2Cl$), 2.40–3.72 (d, J = 8 Hz, C_2—H, C_3—H)
VIa	Cl	Cl	250	71	1550 (C═C, aro), 2970 (CH, ali), 3050 (CH, aro), 1660 (C═O), 1250–1050 (C—O—C), 675 (C—S—C)	6.80–8.25(m, 6H, Ar—H), 3.85 (s, Ar—OCH_3), 3.61 (d, benzothiaza—OCH_3) 4.08 (m, piperazine protons), 2.40–3.73 (d, J = 8 Hz, C_2—H, C_3—H)
VIb	Cl	H	260	76	1520 (C═C, aro), 2985 (CH, ali), 3030 (CH, aro), 1650 (C═O), 1220–1020 (C—O—C), 665 (C—S—C)	6.70–8.40 (m, 7H, Ar—H), 3.70 (s, Ar—OCH_3), 3.59 (d, benzothiaza—OCH_3), 4.15 (m, piperazine protons), 2.40–3.76 (d, J = 8 Hz, C_2—H, C_3—H)
IXa	Cl	Cl	142	73	1250–1050 (C—O—C), 1730 (C═O), 1600 (C═C, aro), 660 (C—S—C)	6.50–8.50 (m, Ar—H), 3.75 (s, Ar—OCH_3), 3.60 (d, benzothiaza—OCH_3), 6.40 (s, C_1'—H)
IXb	Cl	H	145	77	1250–1050 (C—O—C), 1730 (C═O), 1600 (C═C aro), 670 (C—S—C)	6.85–8.40 (m, Ar—H), 3.90 (s, Ar—OCH_3), 3.63 (d, benzothiaza—OCH_3), 6.42, (s, C_1'—H)

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

suggesting the ribosylation at this position. Two sharp absorption bands due to C—O—C linkage asymmetric and symmetric stretching vibrations were observed at 1260–1210 cm^{-1} and 1060–1020 cm^{-1}, respectively, in all the synthesized compounds. The C—H (aliphatic and aromatic), C=C and C—Cl stretching vibrations were observed in the region 3060–2905 cm^{-1}, 1600–1520 cm^{-1} and 780–750 cm^{-1} respectively.

^{1}HNMR

In compounds **III**, the —OH proton was found to be at δ 9.06–9.20 ppm. The >NH protons were observed at δ 8.10–8.30 ppm. All the compounds showed a multiplet due to aromatic protons at δ 6.50–8.70 ppm. The protons of methoxy group attached to aromatic ring were observed at δ 3.59–3.95 ppm. Two characteristic doublets at δ 2.45–2.80 ppm (J = 8 Hz) and δ 3.42–3.73 ppm (J = 8 Hz) were assigned to *cis*-protons at C_2—H and C_3—H of seven-membered ring. The —$COCH_2Cl$ protons were appeared as sharp singlet at δ 4.60–4.70 ppm in compounds **V** while piperazine protons appeared as multiplet in the region δ 4.00–4.50 ppm in compounds **VI**. Compounds **IX**, C_4'—H and >CH_2 protons of sugar moiety caused a multiplet in the region δ 4.10–4.20, while C_2'—H and C_3'—H protons were appeared in the region δ 5.70–5.90 ppm as multiplet protons. C_1'—H caused a singlet at δ 6.40 indicating the β-configuration of sugar.

ANTIMICROBIAL ACTIVITY

All the synthesized compounds were screened for their antimicrobial activity according to Bauer et al.[15] against the bacteria and fungi at concentration 100 μg/disc using Streptomycin and Mycostatin as reference compounds respectively. All the compounds show moderate to fairly good activity against such as *Escherichia coli* (gram −ve bacteria), *Staphylococcus aureus* (gram +ve bacteria), and *Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxysporium* (fungi). The results have presented in Table II in the form of inhibition zones and activity indices. A close look on the activity indices reveals that the ribofuranosides are better antimicrobial agents than their precursors.

EXPERIMENTAL

All the melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on a NICOLET-MEGNA FT-IR 550 spectrophotometer in KBr pallets. The ^{1}HNMR spectra

TABLE II Antimicrobial Activity of 1,5-Benzothiazepines and Their Ribofuranosides[a]

	Inhibition zone (mm)										
Test organism	Standard	**IIIa**	**IIIb**	**IVb**	**IVb**	**Va**	**Vb**	**VIa**	**VIb**	**IXa**	**IXb**
E. coli	10.0	12.0 (1.20)	10.5 (1.05)	12.5 (1.25)	11.5 (1.15)	10.0 (1.0)	13.8 (1.38)	11.5 (1.15)	10.8 (1.08)	12.5 (1.25)	12.9 (1.29)
S. aureus	12.0	14.0 (1.16)	12.5 (1.04)	12.0 (1.0)	12.8 (1.06)	12.2 (1.01)	14.3 (1.19)	12.4 (1.03)	13.8 (1.15)	12.0 (1.0)	12.5 (1.04)
A. niger	22.0	22.5 (1.02)	22.5 (1.02)	24.4 (1.11)	23.0 (1.05)	22.4 (1.02)	22.8 (1.04)	22.0 (1.0)	22.9 (1.04)	23.0 (1.05)	22.5 (1.02)
A. flavus	20.0	22.0 (1.10)	20.5 (1.02)	23.0 (1.15)	20.9 (1.04)	20.9 (1.04)	20.4 (1.02)	20.0 (1.0)	20.4 (1.02)	22.0 (1.10)	23.1 (1.16)
F. oxysporium	23.0	24.0 (1.04)	24.5 (1.06)	25.0 (1.08)	25.4 (1.10)	23.0 (1.0)	25.9 (1.09)	26.0 (1.11)	26.2 (1.13)	23.2 (1.10)	26.0 (1.11)

[a]Values in parentheses represent activity index: Activity index = inhibition area of sample/inhibition area of standard.

were scanned on a FX 90Q JEOL spectrometer using TMS as internal standard (chemical shift in δ, ppm). The purity of compounds were checked by TLC using silica gel "G" as adsorbent and visualization was accomplished by UV light/iodine. 2-Amino-benzenethiols were synthesized by reported methods.

Synthesis of (±)-*cis*-2(4-methoxyphenyl)-3-hydroxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5-benzothiazepin-4[5*H*]-ones III

Methyl-(±)-*cis*-3(4-methoxyphenyl)glycidate **II** (0.01 mol) was stirred with 2-amino-3,5-dichloro/3-chloro-benzenethiol **I** (0.01 mol) in xylene at 160°C for 16–20 h, under nitrogen atmosphere. The reaction mixture was cooled to room temperature and ethanol was added. The product thus separated from mother liquor was collected by filtration, washed with water and recrystallized from ethanol.

Synthesis of (±)-*cis*-2(4-methoxyphenyl)-3-methoxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5-benzothiazepin-4[5*H*]-ones IV

Compounds **III** (0.005 mol), sodiumdithionite (0.25 g) and 10% ethanolic potassium hydroxide solution (55 ml) were reacted with dimethylsulphate (0.014 mol). The reaction mixture was refluxed for 5 h and filtered. The filtrate was poured into ice cold water. The precipitate obtained was filtered, dried, and recrystallized from benzene.

Synthesis of (±)-*cis*-2(4-methoxyphenyl)-3-methoxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5-benzothiazepin-4[5-chloroacetyl]-ones V

Compounds **IV** (0.005 mol) in dry benzene (10.0 ml), a solution of chloroacetylchloride (0.08 mol) in dry benzene was added with stirring at room temperature. The reaction mixture was refluxed for 4 h, and cooled. Benzene was removed under reduced pressure. The residue was chilled and then triturated with petroleum ether (60–80°C). The product thus obtained was recrystallized from ethanol.

Synthesis of (±)-*cis*-2(4-methoxyphenyl)-3-methoxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5-benzothiazepin-4[5-(4′-methylpiperazino-1′)acetyl]-ones VI

A solution of compounds **V** (0.005 mol) in dry benzene (7.5 ml) was treated with N-methylpiperazine (0.013 mol). The reaction mixture was refluxed on a water bath for 5 h, and cooled, the hydrochloride salt

of unreacted amine was removed by filtration. The benzene layer was washed well with water to remove the traces of the unreacted amine. It was then dried over anhydrous sodium sulphate and filtered. Benzene was removed from the filtrate under reduced pressure and the residual solid was recrystallized from ethanol.

Synthesis of (±)-*cis*-2(4-methoxyphenyl)-3-methoxy-6,8-dichloro/6-chloro-2,3-dihydro-1,5- benzothiazepin-4[5-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)]-ones IX

Synthesized compounds **IV** (0.02 mol) were refluxed with HMDS (hexamethyldisilazane) (0.012 mol) along with a few crystals of ammonium sulphate in toluene (30 ml) for 8 h, under anhydrous condition. The coloured solution, thus obtained, was filtered and the solvent was removed under reduced pressure. The sugar viz β-D-ribofuranose-1-acetate-2,3,5-tribenzoate VIII (0.02 mol) was added to the above pasty mixture and was stirred at 155–160°C under vacuum for 15 min in absence of moisture. The reaction mixture was stirred 10 h. During the reaction period, the vacuum was regularly applied for 5 min at the end of every hour. The melt was boiled in methanol for 10 min, cooled, and filtered. The solid mass of ribofuranosides **IX** thus obtained was recrystallized from diethylether.

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