Heteroatom Chemistry
Volume 13, Number 7, 2002

Syntheses of Some New 1,5-Benzothiazepine Derivatives and Their Ribofuranosides as Antimicrobial Agents

Girwar Singh, Neeraj Kumar, Ashok K. Yadav, and A. K. Mishra

Department of Chemistry, University of Rajasthan, Jaipur 302004, India

Received 10 September 2001; revised 22 October 2001

ABSTRACT: *(±)-*cis*-2-(4-Methoxyphenyl)-3-hydroxy/methoxy-6-ethoxy/phenoxy-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-ethoxy/phenoxybenzenethiol with methyl-(±)-*trans*-3-(4-methoxyphenyl)glycidate in xylene. Ribofuranosides, viz. (±)-*cis*-2-(4-methoxyphenyl)-3-methoxy-6-ethoxy/phenoxy-2,3-dihydro-1,5-benzothiazepin-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 a derivative, sugar, viz.* β-D-*ribofuranose-1-acetate-2,3,5-tribenzoate, in toluene in vacuo. The structures of all the synthesized ribofuranosides and their precursors have been characterized on the basis of elemental analyses and IR, ^{1}H NMR, and ^{13}C NMR spectral data. These compounds were screened for their antimicrobial activity.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:620–625, 2002; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10051

INTRODUCTION

An intensive survey of the literature revealed that 1,5-benzothiazepines have potential chemotherapeutic importance as anticancer [1], antihypertensive [2], and antibacterial [3] agents. Many pharmacological compositions of 1,5-benzothiazepines have been patented [4,5] and some of the well-known drugs are thiazesim [6], diltiazem [7], and clentiazem [8]. Krapcho et al. [9] have also studied the ability of 1,5-benzothiazepine derivatives to function as a CNS depressant. A survey reveals that the reaction of silylated heterocyclic bases with sugars has become a standard synthetic method for the synthesis of nucleosides [10]. Keeping this in view and as a continuation of our earlier work [11], we wish to report here the syntheses of some new 1,5-benzothiazepines and their ribofuranosides in search of new medicinally important drugs.

RESULTS AND DISCUSSION

Syntheses of (±)-*cis*-2-(4-methoxyphenyl)-3-hydroxy-6-ethoxy/phenoxy-2,3-dihydro-1,5-benzothiazepin-4[5*H*]-ones **III** were carried out by the condensation of 2-amino-3-ethoxy/phenoxy-benzenethiols **I** with methyl-(±)-*trans*-3(4-methoxyphenyl)glycidate **II** in xylene at 160°C, for 20–25 h, under a nitrogen atmosphere in 82–85% yields. We have investigated the effect of the solvent and temperature on the reaction of the *trans*-glycidate **II** with various substituted benzenethiols in the absence of a catalyst. The temperature had a surprisingly large effect on the stereochemistry of ring opening to the *trans*-glycidate **II**. The *cis*-opening product of compound **III** appeared to form via the *threo*-ester. These observations are in agreement with earlier work [12], which reported that *erythro*-ester is thus formed only in the presence of a catalyst. Treatment of compounds **III** with dimethyl sulphate afforded (±)-*cis*-2-(4-methoxyphenyl)-3-methoxy-6-ethoxy/phenoxy-2,3-

Correspondence to: A. K. Mishra; e-mail: kudiwal@datainfosys.net.
Contract grant sponsor: UGC, Bhopal.

dihydro-1,5-benzothiazepin-4[5*H*]-ones **IV**. Compounds **IV** on treatment with chloroacetyl chloride gave (±)-*cis*-2-(4-methoxyphenyl)-3-methoxy-6-ethoxy/phenoxy-2,3-dihydro-1,5-benzothiazepin-4-[5-chloroacetyl]-ones **V**, which in turn afforded (±)-*cis*-2-(4-methoxyphenyl)-3-methoxy-6-ethoxy/phenoxy-2, 3-dihydro-1,5-benzothiazepin-4-[5-(4′-methylpiperazino-1′)acetyl]-ones **VI**, on reaction with *N*-methylpiperazine. Compound **IV**, on treatment with hexamethyldisilazane in the presence of ammonium sulphate produced the corresponding trimethylsilyl derivatives **VII**, which, when stirred with β-D-ribofuranose-1-acetate-2,3,5-tribenzoate **VIII**, in toluene in vacuo at 155–160°C, for 10 h., gave the corresponding ribofuranosides, viz. (±)-*cis*-2-(4-methoxyphenyl)-3-methoxy-6-ethoxy/phenoxy-2, 3-dihydro-1,5-benzothiazepin-4-[5-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)]-ones **IX** (Scheme 1).

The results of spectroscopic data are discussed below.

SPECTRAL STUDIES

IR Spectra

In compounds **III**, a broad band in the region of 3550–3110 cm^{-1} was observed because of >NH and —OH stretching. Compounds **IV** showed a less broad band in the region 3460–3120 cm^{-1} because of the presence of only one >NH group. This band was absent in compounds **V, VI**, and **IX**. The >C—S—C< linkage of the seven-membered ring caused a weak and sharp absorption band in the region 690–640 cm^{-1}. The >C=O group was observed as a sharp and strong band at 1730–1650 cm^{-1} in all of the synthesized compounds. Two sharp absorption bands due to the >C—O—C< linkage, asymmetric and symmetric stretching vibrations, were observed in the region 1270–1210 cm^{-1} and 1065–1010 cm^{-1}, respectively, in all the synthesized compounds. In compounds **IX**, the >NH band has completely vanished, suggesting the ribosylation at this position.

^{1}H NMR Spectra

In compounds **III**, the —OH proton was found to be at δ 9.10–9.20. The proton of the >NH group was observed in the region δ 8.12–8.30 in compounds **III** and **IV**. The phenoxy group appeared as a multiplet at δ 6.85–7.60 because of phenyl protons, and ethoxy protons revealed their presence by a triplicate at δ 1.32–1.38, along with a quartet at δ 3.96–3.98 because of $-CH_3$ and $-CH_2$ protons. The protons of the methoxy group attached to the aromatic rings were observed at δ 3.72–3.85 in all of the synthesized compounds. Two characteristic doublets at δ 2.46–2.80 ($J = 8$ Hz) and δ 3.40–3.60 ($J = 8$ Hz) were assigned to *cis*-protons of C_2—H and C_3—H of the seven-membered ring. The $COCH_2Cl$ protons appeared as sharp singlets at δ 4.60–4.70 in compounds **V**, while piperazine protons were observed at δ 4.0–4.50 in compounds **VI**. All the compounds showed a multiplet in the region δ 6.85–8.30 because of aromatic protons. In compounds **IX**, C_2'—H and C_3'—H protons appeared in the region δ 5.60–5.70 as multiplets. The C_1'—H protons of the sugar moiety caused a singlet in the region δ 6.40–6.45, indicating the β-configuration of the compounds **IX**.

The ^{13}C NMR data of compounds **III** and **IX** are presented in the Table 1 and these data are in reasonable agreement with their structures.

^{13}C NMR Spectra

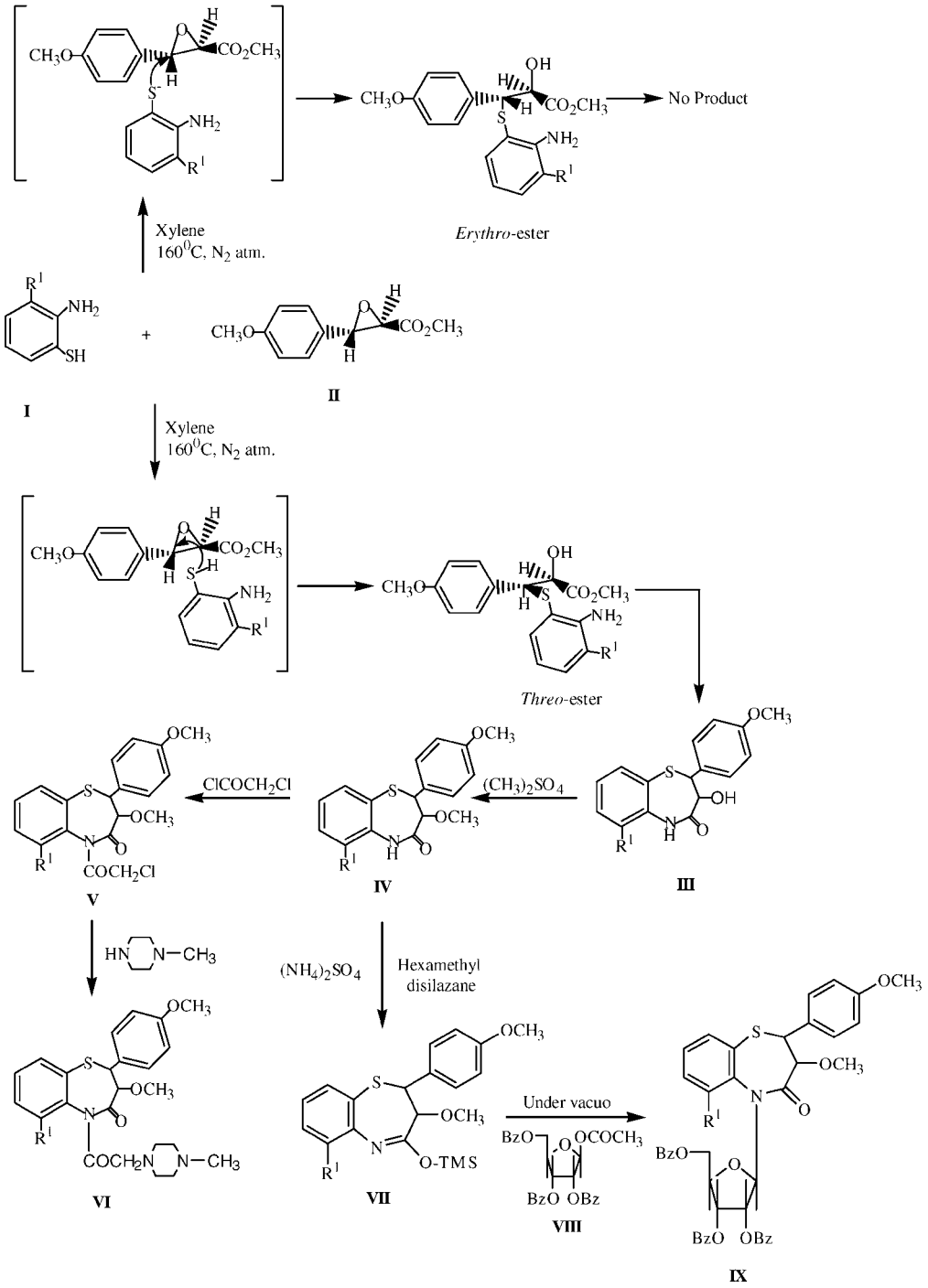
In the ^{13}C NMR data, a signal between δ 173 and δ 164 was ascribed to be due to the carbon of >C=O (C-4). All aromatic carbons, including those attached to the sugar moiety, appeared at δ 120.4–148.5.

ANTIMICROBIAL ACTIVITY

All of the synthesized 1,5-benzothiazepine derivatives and their ribofuranosides were screened for their antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* (bacteria) and *Aspergillus niger*, *Aspergillus flavus*, and *Fusarium oxysporium* (fungi) at the concentration of 100 μg/disc in agar media following the paper disc method of Gould and Bowie [13]. Streptomycin and mycostatin were used as the reference compounds for antibacterial and antifungal activity, respectively. Observations of Table 2 reveal that the compound **IIIa** showed equal activity against *F. oxysporium*, while **IIIb** demonstrated less activity against *E. coli*. Further, in compounds **IVa** and **IVb**, the latter showed better activity against *E. coli*. The ribofuranosides showed better antimicrobial activity than their precursors, except in the case of ribofuranosides **IXa** against *A. flavus*, *E. coli*, and *S. aureus*. These results have been tabulated in the form of inhibition zone (mm) and activity indices (Table 2).

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr pellets on a NICOLET-MEGNA FT-IR 550 spectrophotometer. The ^{1}H NMR spectra were obtained on an FX 90Q JEOL spectrometer



SCHEME 1

in $CDCl_3$/DMSO-d_6, and ^{13}C NMR spectra were recorded in DMSO solution, using TMS as an internal standard (chemical shift in δ). The purity of compounds was checked by TLC using gel "G" as adsorbent, and visualization was accomplished by UV light/iodine. 2-Amino-benzenethiols were synthesized by reported methods.

Syntheses of (±)-cis-2-(4-Methoxyphenyl)-3-hydroxy-6-ethoxy/phenoxy-2,3-dihydro-1,5-benzothiazepin-4[5H]-ones **III**

Methyl-(±)-*cis*-3-(4-methoxyphenyl)glycidate **II** (0.01 mol) was stirred with 2-amino-3-ethoxy/phenoxy-benzenethiol **I** (0.01 mol) in xylene at 160°C

TABLE 1 The IR, ^{1}H NMR, and ^{13}C NMR Spectral Data of 1,5-Benzothiazepines and Their Ribofuranosides

Compound[a]	*IR (KBr:ν_{max} cm^{-1})*	*^{1}H NMR (δ, ppm from TMS)*	*^{13}C NMR (δ, ppm from TMS)*
IIIa	3540–3110 (NH/OH), 1650 (C═O), 1250–1030 (C—O—C), 670 (C—S—C), 1590 (C═C, aro), 2920 (CH, ali), 3060 (CH, aro)	8.20 (s, NH), 6.90–7.75 (m, 7H, Ar—H), 3.72 (s, Ar—OCH_3), 9.20 (s, OH), 2.50–3.50 (d, $J = 8$ Hz, C_2—H, C_3—H), 1.32 (t, —CH_3 of OC_2H_5), 3.95 (q, —CH_2 of OC_2H_5)	C-2 (153.26), C-3 (164.6), 55.2 (OCH_3), 168.9 (C═O), 120.42–140.16 (11, Ar—C)
IIIb	3550–3120 (NH/OH), 1660 (C═O), 1260–1050 (C—O—C), 660 (C—S—C), 1580 (C═C, aro), 2930 (CH, ali), 3040 (CH, aro)	8.30 (s, NH), 6.85–7.80 (m, 11H, Ar—H), 3.75 (s, Ar—OCH_3), 9.10 (s, OH), 2.51–3.55 (d, $J = 8$ Hz, C_2—H, C_3—H)	C-2 (154.10), C-3 (164.10), 54.40 (OCH_3), 167.12 (C═O), 121.10–142.16 (11, Ar—C)
IVa	3460–3140 (NH), 1670 (C═O), 1260–1070 (C—O—C), 665 (C—S—C), 1570 (C═C, aro), 2925 (CH, ali), 3035 (CH, aro)	8.15 (s, NH), 6.90–7.90 (m, 7H, Ar—H), 3.80 (s, Ar—OCH_3), 3.69 (d, OCH_3 benzothiaz.), 2.46–3.45 (d, $J = 8$ Hz, C_2—H, C_3—H), 1.35 (t, —CH_3 of OC_2H_5), 3.96 (q, —CH_2 of OC_2H_5)	
IVb	3430–3120 (NH), 1680 (C═O), 1265–1025 (C—O—C), 650 (C—S—C), 1585 (C═C, aro), 2950 (CH, ali), 3060 (CH, aro)	8.12 (s, NH), 6.85–8.00 (m, 11H, Ar—H), 3.85 (s, Ar—OCH_3), 3.65 (d, OCH_3 benzothiaz.), 2.47–3.56 (d, $J = 8$ Hz, C_2—H, C_3—H)	
Va	1690 (C═O), 1250–1030 (C—O—C), 675 (C—S—C), 760 (C—Cl), 1575 (C═C, aro), 2910 (CH, ali), 3060 (CH, aro)	6.90–8.05 (m, 7H, Ar—H), 3.85 (s, Ar—OCH_3), 3.62 (d, OCH_3 benzothiaz.), 4.60 (s, —CH_2 of $COCH_2Cl$), 2.52–3.60 (d, $J =$ 8 Hz, C_2—H, C_3—H), 1.38 (t, —CH_3 of C_2H_5), 3.98 (q, —CH_2 of C_2H_5)	
Vb	1685 (C═O), 1265–1020 (C—O—C), 670 (C—S—C), 765 (C—Cl), 1565 (C═C, aro), 2935 (CH, ali), 3025 (CH, aro)	6.92–8.10 (m, 11H, Ar—H), 3.82 (s, Ar—OCH_3), 3.65 (d, OCH_3 benzothiaz.), 4.70 (s, —CH_2 of $COCH_2Cl$), 2.53–3.58 (d, $J =$ 8 Hz), C_2—H, C_3—H)	
VIa	1680 (C═O), 1265–1045 (C—O—C), 645 (C—S—C), 1525 (C═C, aro), 2980 (CH, ali), 3050 (CH, aro)	6.87–8.03 (m, 7H, Ar—H), 3.79 (s, Ar—OCH_3), 3.64 (d, OCH_3 benzothiaz.), 2.54–3.56 (d, $J = 8$ Hz, C_2—H, C_3—H), 4.50 (m, piperazine proton), 1.35 (t, —CH_3 of OC_2H_5), 3.96 (q, —CH_2 of OC_2H_5)	
VIb	1685 (C═O), 1270–1030 (C—O—C), 660 (C—S—C), 1550 (C═C, aro), 2970 (CH, ali), 3065 (CH, aro)	6.88–8.10 (m, 11H, Ar—H), 3.85 (s, Ar—OCH_3), 3.67 (d, OCH_3 benzothiaz.), 2.55–3.50 (d, $J = 8$ Hz, C_2—H, C_3—H), 4.20 (m, piperazine protons)	
VIa	1730 (C═O), 1270–1020 (C—O—C), 690 (C—S—C), 1620 (C═C, aro)	6.85–8.30 (m, Ar—H), 3.76 (s, Ar—OCH_3), 3.68 (d, OCH_3 benzothiaz.), 6.40 (C_1'—H, s)	
IXa			C-2 (154.80), C-3 (165.10), 54.80 (OCH_3), 172.32 (C═O), 120.42–145.12 (17, Ar—C), 125.82–136.20 [Ar—C(OBz)]
IXb	1720 (C═O), 1260–1010 (C—O—C), 685 (C—S—C), 1610 (C═C, aro)	6.90–8.25 (m, Ar—H), 3.82 (s, Ar—OCH_3), 3.66 (d, OCH_3 benzothiaz.), 6.45 (C_1'—H, s)	C-2 (155.12), C-3 (165.62), 54.90 (OCH_3), 171.10 (C═O), 122.12–148.5 (17, Ar—C), 126.09–136.82 [Ar—C(OBz)]

[a] The elemental analyses (C,H, and N) were found in reasonable agreement with the calculated values.

TABLE 2 Antimicrobial Activity of Synthesized 1,5-Benzothiazepines and Their Ribofuranosides

	Bacteria		*Fungi*		
Compound No.	Escherichia coli *(Gram negative)*	Staphylococcus aureus *(Gram positive)*	Aspergillus niger	Aspergillus flavus	Fusarium oxysporium
IIIa	11.0 (1.10)	13.5 (1.12)	23.0 (1.04)	21.0 (1.05)	23.0 (1.0)
IIIb	9.0 (0.90)	11.0 (0.92)	25.0 (1.14)	22.5 (1.12)	23.5 (1.02)
IVa	10.5 (0.98)	14.5 (1.21)	24.0 (1.09)	21.9 (1.09)	22.8 (0.99)
IVb	11.9 (1.19)	12.5 (1.04)	22.0 (1.0)	20.0 (1.0)	22.5 (1.11)
Va	12.0 (1.20)	11.8 (0.98)	22.6 (1.03)	22.8 (1.14)	23.9 (1.03)
Vb	12.5 (1.25)	12.5 (1.04)	23.8 (1.08)	23.2 (1.16)	24.8 (1.07)
VIa	10.5 (1.05)	11.9 (0.99)	23.5 (1.07)	23.5 (1.17)	25.6 (1.11)
VIb	10.2 (1.02)	13.4 (1.12)	22.6 (1.03)	19.8 (0.99)	23.2 (1.01)
IXa	12.0 (1.20)	13.0 (1.08)	25.6 (1.16)	19.5 (0.99)	25.6 (1.11)
IXb	12.5 (1.25)	14.5 (1.21)	24.8 (1.13)	24.0 (1.20)	25.1 (1.09)

Values in paranthesis represent activity index. Activity index = inhibition area of sample/inhibition area of standard.

for 20–25 h, under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and ethanol was added. The product that separated from the mother liquor was collected by filtration, washed with water, dried, and recrystallized from ethanol.

IIIa: $R^1 = -OC_2H_5$, m.p. = 190°C, yield = 85%.

IIIb: $R^1 = -OC_6H_5$, m.p. = 180°C, yield = 82%.

Syntheses of (±)-cis-2-(4-Methoxyphenyl)-3-methoxy-6-ethoxy/phenoxy-2,3-dihydro-1,5-benzothiazepin-4[5H]-ones **IV**

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

IVa: $R^1 = -OC_2H_5$, m.p. = 215°C, yield = 77%.

IVb: $R^1 = -OC_6H_5$, m.p. = 220°C, yield = 78%.

Syntheses of (±)-cis-2-(4-Methoxyphenyl)-3-methoxy-6-ethoxy/phenoxy-2,3-dihydro-1,5-benzothiazepin-4-[5-chloroacetyl]-ones **V**

To compounds **IV** (0.005 mol) in dry benzene (10.0 ml), a solution of chloroacetyl chloride (0.08 mol) in dry benzene was added, with stirring at room temperature. Each 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.

Va: $R^1 = -OC_2H_5$, m.p. = 150°C, yield = 74%.

Vb: $R^1 = -OC_6H_5$, m.p. = 145°C, yield = 70%.

Syntheses of (±)-cis-2-(4-Methoxyphenyl)-3-methoxy-6-ethoxy/phenoxy-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). Each reaction mixture was refluxed on a water bath for 5 h and cooled; and the hydrochloride salt of the 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.

VIa: $R^1 = -OC_2H_5$, m.p. = 240°C, yield = 75%.

VIb: $R^1 = -OC_6H_5$, m.p. = 270°C, yield = 73%.

Syntheses of (±)-cis-2-(4-Methoxyphenyl)-3-methoxy-6-ethoxy/phenoxy-2,3-dihydro-1,5-benzothiazepin-4-[5-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)]-ones **IX**

Compounds **IV** (0.02 mol) were refluxed with hexamethyldisilazane (0.012 mol) along with a few crystals of ammonium sulphate in toluene (30 ml) for 8 h, under anhydrous conditions. Each grey-colored mixture, thus obtained, was filtered and the solvent was removed from the filtrate under reduced pressure. The sugar, viz. β-D-ribofuranose-1-acetate-2,3,5-tribenzoate (0.02 mol), was added to the above

pasty mixture and was stirred at 155–160°C under vacuum for 15 min in the absence of moisture. The reaction mixture was stirred for 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 each ribofuranoside **IX** thus obtained was recrystallized from diethyl ether.

IXa: $R^1 = -OC_2H_5$, m.p. = 138°C, yield = 80%.

IXb: $R^1 = -OC_6H_5$, m.p. = 130°C, yield = 76%.

All of the synthesized compounds have been characterized on the basis of spectral studies (IR, ^{1}H NMR, ^{13}C NMR) and elemental analyses (Table 1).

REFERENCES

[1] Mulvinill, M. J.; Miller, M. J. Tetrahedron 1998, 54, 716.

[2] Narita, H.; Otsuka, M.; Yobana, H.; Nagao, T. J. Pharmacobio Dyn 1986, 9(6), 547.

[3] Sharma, A. K.; Singh, G.; Yadav, A. K.; Prakash, L. Molecules 1997, 2, 129.

[4] Rossey, G.; Chekroun, I.; Ugolini, A.; Wick, A.; Gerin, B.; Bourbon, A.; Aurax, J. B. Eur Pat Appl EP 378, 455 (Cl.CO7D280/10), July 18, 1990; FR Appl 89/246, Jan. 11, 1989, 7 pp.; Chem Abstr 1992, 116, 83706.

[5] Takeda, M.; Ohishi, J.; Nakajima, H.; Nagao, J. Eur Pat Appl EP 182, 273 (Cl.CO7D281/10), May 28, 1986 (Tanabe Seiyaku Co. Ltd.); GB Appl 84/29, 102, Nov. 17, 1984, 41 pp.; Chem Abstr 1986, 105, 13391.

[6] Geyer, H. M.; Watzman, N.; Buckley, J. P. J Pharm Sci 1970, 59(7), 964; Chem Abstr 1970, 73, 75424.

[7] Kantoci, D.; Murray, E. D.; Quiggle, D. D.; Wechter, W. J. J Med Chem 1996, 39, 1196.

[8] Kikkawa, K.; Murata, S.; Iwasaki, H.; Toriumi, W.; Banno, K.; Nagao, T. Arzneium-Forsch 1992, 42(6), 781.

[9] Krapcho, J.; Turk, C. F.; Piala, J. J. J Med Chem 1968, 11(2), 361.

[10] Attia, A. M.; Elgemeie, G. H.; Shahada, L. A. Tetrahedron 1997, 53(51), 17441.

[11] Singh, G.; Kumar, N.; Sharma, A. K.; Prakash, L. Res Chem Intermed 2000, 26(5), 445.

[12] Tomiki, H.; Hirozumi, I.; Mikihiko, K.; Mikio, T. J Chem Soc, Perkin Trans 1 1984, 1725.

[13] Gould, J. C.; Bowie, J. H. Edinb Med J 1950, 59, 178.