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Cyclic Sulfites, Key Intermediates in Synthesis of 1-Alkylamino-3-aryloxy-2-propanols from Glycidol

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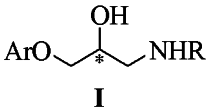
Abstract—A number of 3-aryloxypropanedioles were obtained by treating glycidol with phenols. The latter with thionyl chloride afforded 4-aryloxymethyl-1,3,2-dioxathiolane 2-oxides. These compounds were also obtained from 4-chloromethyl-1,3,2-dioxathiolane 2-oxides by substitution aryloxy group for chlorine. The cyclic sulfides synthesized are universal intermediates in the synthesis of chiral aryloxypropanolamines among which are known β-adrenoblockaders, cardiovascular drugs. From (S)-glycidol, (S)-alprenolol, (S)-propanolol, and (S)-thymolol were synthesized.

Chiral aryloxypropanolamines **I** are abundant among the series of β-adrenoblocaders, cardiovascular drugs [1].



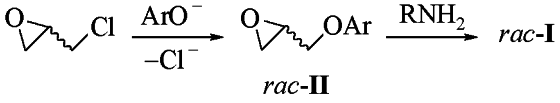
I

R = *i*-Pr, *t*-Bu.

It is shown that *S*-isomers in this series serve as eutomers (enantiomers producing the desired effect) [2]. Therewith, the *R*-isomers turn out to be distomers, namely, at best an inert substance, but, more frequently, an ingredient with unwanted side activity. The main trend in modern medicinal chemistry and pharmaceutical industry is substitution of racemic substances with enantiopure ones [3]. Although some β-adrenoblockaders (e.g.,thymolol, levobetacsolol) have been already produced as pure eutomers, the majority of the drugs are racemic mixtures. Thus, the problem of synthesizing aryloxypropanolamines **I** as enantiopure or enriched with one of enantiomer compounds is still urgent.

The main industrial production process of racemic β-adrenoblockaders consists in preparation of glycidyl aryl ethers **II** from epichlorohydrin followed by opening of the oxirane ring by primary amine [4].

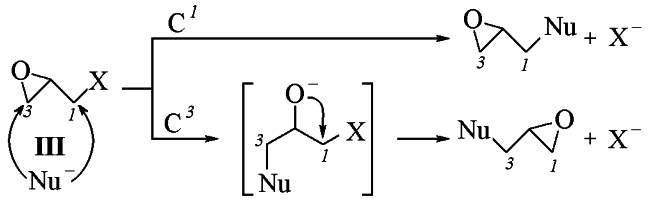
Scheme 1.



rac-**II**

Unfortunately this scheme loses its advantages of being simple and economically feasible as soon as the target products should be enriched with a single enantiomer. Firstly, enantiopure epichlorohydrin is not a cheap and accessible compound [5]. Secondly, the C^1-activated 2,3-epoxypropanes **III** are known [6] not to react with nucleophiles in an unambiguous fashion: alongside the normal attack on the C^1 atom occurs attack on the C^3 atom with opening and subsequent closure of the oxirane ring.

Scheme 2.



At different substitution paths the final products have the opposite configuration of the chiral C^2 atom. Thus the simultaneous reaction in both directions results in partial racemization of the target products. With epichlorohydrin (**IIIa**, X = Cl) and phenoxide ion as nucleophile ~90% of product **IIa** (Ar = Ph) originates from attack on C^3 atom [6, 7]. The presence in the mixture of ~10% of the "normal" product and no means to block the nucleophilic substitution at the C^1 atom prevent production along Scheme 1 final products of high enantiomeric excess without additional purification even from enantiopure compound **IIIa**.

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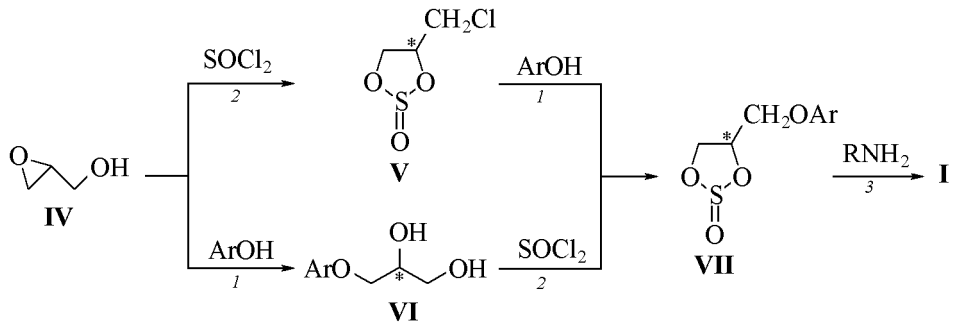
Scheme 3.



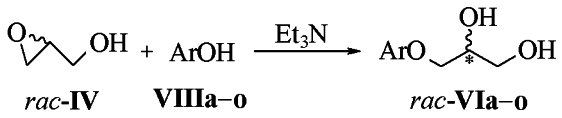
The presence in the molecules of epoxypropanes **III** better leaving groups than Cl^- makes possible a predominant nucleophilic substitution at C^1 atom. For instance, the reaction between enantiopure glycidyl tosylate (**IIIb**, X = *p*-$CH_3C_6H_4SO_3$) and various phenols in alkali medium afforded ethers **II** with predominantly conserved configuration; however, the enantiomeric purity of the final products varied within a wide range [8]. A single direction of reaction and high enantiomeric purity of ethers **II** was achieved at the use of glycidol triflates (**IIIc**, X = CF_3SO_3) and nitrobenzenesulfonates (**IIId**, X = *m*-$NO_2C_6H_4SO_3$) [6–8] but the scaling of the processes is prevented by the high price of the activating reagents and an additional stage of preparation of compounds **IIIc, d** from the enantiomerically enriched glycidol. Thus the alternative routes to aryloxypropanolamines are still required that should within a unified synthetic operations sequence ensure production of a set of compounds with desired configurations by variation of a limited number of parameters [9].

In the present research was investigated the possibility of application to this problem of cyclic sulfites, epoxy-like compounds that were extensively studied recently [10]. As a starting compound we selected glycidol (**IV**) that is relatively cheap in the enantioenriched state and available both on laboratory and industrial scale [5]. The general sequence of glycidol (**IV**) conversions into aryloxypropanolamine **I** is presented in Scheme 3.

The preparation of 4-chloromethyl-1,3,2-dioxathiolane 2-oxides (**V**) by direct treating glycidol with thionyl chloride we developed previously [11]. The process did not require any auxiliary reagents, and the yield of compound **V** approached 90%. From glycidol (*S*)-**IV** dioxathiolane (4*S*)-**V** formed with conservation of the enantiomeric composition of the initial glycidol. The pyramidal structure of tricoordinate sulfur atom led to formation of diastereomeric *cis*- and *trans*-dioxathiolanes **V**, but the separation of the mixture was not required for the following reactions.

Within the framework of the scheme under consideration the aromatic fragment can be introduced in two ways;: firstly, by nucleophilic substitution of chlorine in sulfites **V** by aryloxide anions. The process was previously regarded as proceeding abnormally and resulting in symmetrical 5-aryloxy-1,3,2-dioxathiolanes [12, 10]. We demonstrated that this statement arose from the erroneous treatment of the experimental data, and in the aprotic solvents the racemic sulfites **V** reacted with phenoxide anion giving rise to 4-phenoxymethyl-1,3,2-dioxathiolanes *rac*-**VIIa** [13]. The enantiomerically enriched chloromethylsulfites (4*S*)-**V** under these conditions give (4*R*)-aryloxymethylsulfites with the same enantiomeric ratio as in the initial product. It was shown by examples of reactions with 1-naphthol (**VIIIb**) and 4-(N-morpholino)-3-hydroxy-1,2,5-thiadiazole (**VIIIc**) [14]. In this study the generalality of the process was confirmed by preparation of sulfite *rac*-**VIId** from dioxathiolane *rac*-**V** and 2-allylphenol (**VIIId**) in toluene. An alternative approach to aryloxymethylsulfites **VII** consists in the reversed order of reactions: first phenols are added to glycidol, and then the arising diols are treated with $SOCl_2$. It is known that direct reaction between glycidol and phenols is slow and affords a mixture of 3-aryloxypropane-1,2,-diols (**VI**) with their structural isomers 2-aryloxypropane-1,3-diols [6]. However in the presence of such catalysts as $Ti(OAlk)_4$ [15], Alk_3N [16], or CsF [8] the addition of ArOH occurs regioselectively providing the desired isomers **VI**. In our study we followed the suggestions from [16] and used Et_3N as a catalyst for phenols addition to glycidol **IV**. At first we used racemic glycidol for the main problem here was the regioselectivity of addition. The data obtained with a series of phenols are given in Table 1. All diols **VIa–o** thus obtained had in the

Table 1. Yields, boiling (melting) points of reaction products from *rac*-glycidol and phenols



rac-**IV** **VIIIa–o** *rac*-**VIa–o**

rac-VI	Ar	Yield, %	bp, °C (*p*, mm Hg)	mp, °C	Publ. mp, °C
VIa	Ph	70	105–110 (0.03)	51–53	54.8 [22, p. 589]
VIb	1-Naphthyl	91	–	99–101	99 [22, p. 4214]
VIc	5-Morpholino-2,1,3-thiadiazolyl-4	30		89–91	–
VId	2-AllylC_6H_4	77	145–147 (0.01)	43–44	–
VIe	3-MeOC_6H_4	74	148–150 (0.05)	70–71	73.0–73.5 [22, p. 5671]
VIf	4-MeC_6H_4	63		73–74	73–74
VIg	4-MeOC_6H_4	60		82–83	80.5–81.5 [22, p. 5736]
VIh	4-BrC_6H_4	71		80–81	84–85 [22, p. 1049]
VIi	4-IC_6H_4	72		99–101	
VIj	4-*t*-BuC_6H_4	73		84–86	83–84 [22, p. 3302]
VIk	4-$NO_2C_6H_4$	50	150–155 (0.05)		58 [23]
VIl	2,4-$Cl_2C_6H_3$	33		81–82	81–82 [22, p. 895]
VIm	2,4,6-$Me_3C_6H_2$	69	149–153 (0.05)	58–60	60–62 [22, p. 3255]
VIn	2,6-Me_2-4-ClC_6H_2	62	140–143 (0.05)	63–64	64.5–65.0 [22, p. 3122]
VIo	2,6-Me_2-4-BrC_6H_2	55	178–180 (0.05)	62–63	–

Table 2. Characteristics of enantio-enriched 3-aryloxypropane-1,2-diols (*S*)-(**VIa**–**d, g**)

Compd. no.	mp, °C	Publ. mp, °C	$[\alpha]_D^{20}$	Publ. $[\alpha]_D^{25}$
(*S*)-(**VIa**)	63–64	62.5–64.5[a] [8]	9.1 (*c* 1.7, 95% EtOH)	–9.5[a] (*c* 0.5, MeOH) [8]
(*S*)-(**VIb**)	111–113	110–112 [19], 112.4[a] [16]	7.5 (*c* 1.0, MeOH)	7.6 (*c* 1.0, MeOH) [19]
(*S*)-(**VIc**)	118–120	–	18.2 (*c* 0.9, 95% EtOH)	–
(*S*)-(**VId**)	47–49	–	–2.1 (*c* 2.8, EtOH)	–
(*S*)-(**VIg**)	79–80	80.0[a] [16]	7.4 (*c* 1.3, MeOH)	7.9 (*c* 1.0, EtOH) [24]

[a] For (*R*)-enantiomer.

^{13}C NMR spectra a characteristic group of signals belonging to nonsymmetrically substituted fragment $ArOCH_2$-CH-CH_2OH at δ 63.2±0.8 (CH_2OH), 69.8±1.3 ($ArOCH_2$) and 70.1±0.8 ppm (CHOH). The symmetrically substituted 2-phenoxypropane-1,3-diol, isomer of diol **VIa**, we previously obtained by indirect procedure [13]. This compound is characterized by the following signals in the aliphatic part of the ^{13}C NMR spectrum: δ 78.85 (PhOCH) and 61.97 ppm (CH_2OH). Therefore the lack of signals at δ > 75 ppm in the ^{13}C NMR spectra of compounds **VIa–o** evidences that all the studied phenols added regioselectively to glycidol under conditions described.

The yields in Table 1 correspond to the isolated final reaction product and also reflect the difficulty of its purification (of crystallization etc.). Still it should be noted that in general the yields are regularly smaller for phenols with electron-withdrawing substituents (**VIIIk, l**), and also for the hydroxy derivative of the π-electrons-deficient 1.2.5-thiadiazole (**VIIIc**). In these and similar cases the opening of the epoxy ring occurs slowly, requires higher temperature, is accompanied by tarring and is not complete. As a result the final products contain the initial compounds as impurities. Thus on the preparative scale this reaction should be recommended for phenols with donor substituents since diols **VI** obtained therefrom easily crystallize.

The latter factor is especially important in the synthesis of enantioenriched 3-aryloxypropane-1,2-diols for crystallization as a rule increases their ee factor. The initial glycidol (*S*) of *ee* 90.1% we prepared by enantioselective epoxidation of allyl alcohol by Sharpless method [17]. The reactions of glycidol (*S*)-(**IV**) with phenols **VIIIa–d, g** were carried out under the conditions developed for *rac*-glycidol. The characteristics of compounds **VIa–d, g** are given in Table 2.

The conversion of diols **VI** into sulfites **VII** occurs virtually quantitatively by treating them with an equivalent amount of $SOCl_2$ in CH_2Cl_2 at cooling. As a rule there was no need to bind the liberating HCl, and thus we added Et_3N to the reaction mixture only with morpholino-containing diol **VIc**.

Sulfites **VII** prepared by different procedures have somewhat dissimilar diastereomeric composition, i.e. unlike ratio of *cis*- and *trans*-isomers. Diastereomeric composition of the final aryloxymethyl derivatives obtained from a mixture of *cis*- and *trans*-dioxathiolanes **V** is close to that of initial compounds, 1 : 1. The reaction of $SOCl_2$ with diols also in general is not stereoselective and affords commonly a mixture of *cis*- and *trans*-aryloxymethylsulfites, the *trans*-isomer a little prevailing. A special case presents *p*-bromophenoxy derivative *rac*-**VIIh**. According to ^1H and ^{13}C NMR spectra, already in the product separated from the reaction mixture the ratio of *trans*- to *cis*-isomer is over 20 : 1. After a single recrystallization diol *trans*-**VIh** was separated as virtually individual compound. The diastereomeric composition of the aryloxymethylsulfites apparently is not important for further transformations. However we wished to mention the exclusive and not yet understandable diastereoselectivity in a reaction trivial in all the other respects.

Apart of the signals of aromatic moieties the ^{13}C NMR spectra of all sulfites **VII** obtained by us have similar characteristics. The signals of endocyclic CH carbon appear in the range 78 ± 0.5 and 80.2 ± 0.7 ppm for *trans*- and *cis*-isomers respectively. Endocyclic CH_2 atom gives signals at 69.0 ± 1.1 (*trans*) and 79.4 ± 1.6 ppm (*cis*). Finally, signals at 67.5±1.2 (*trans*) and 68.5±1.2 ppm (*cis*) belong to exocyclic methylene carbon in OCH_2 group. The only exception from the general trend is the ^{13}C NMR spectrum of the 1,2,5-thiadiazole derivative *cis*-**VIIc** where the chemical shifts of the endocyclic methine carbon CH (69.67 ppm) and of the carbon in exocyclic fragment OCH_2 (46.14 ppm) are shifted by more than 10 ppm from the average values. Therewith the signals of the remaining unit in the three-carbon fragment of aryloxymethylsulfite, endocyclic CH_2 (71.68 ppm), and also the signals of dioxathiolane oxide *trans*-**VIIc** (77.77, 68.26, and 69.08 in the same sequence as for *cis*-**VIIc**) correspond to the general regularity. The upfield shift of signals from two carbons nearest to the substituent is apparently due to magnetically anisotropic effect of 1,2,5-thiadiazole ring in certain conformation specific for the *cis*-isomer.

The final stage of the synthesis for aryloxypropanolamines **I** from sulfites **VII** by direct treatment with primary amines for racemic compounds is described in a patent [18]. The same procedure was applied to preparation of enantio-enriched β-adrenoblockaders, (1*S*)-propanolol (*S*)-(**Ib**, R = *i*-Pr) [19, 11, 14] and (*S*)-thymolol (*S*)-(**Ic**, R = *t*-Bu) [14]. We prepared the same products and also one more practically important β-adrenoblockader, alprenolol (**Id**, R = *i*-Pr), in the enantio-enriched state, following the sequence of transformations *1*, *2*, *3* from Scheme 3. The target product (*S*)-**Id** was isolated in 73% yield at boiling sulfite (4*R*)-**VIId** with excess *i*-$PrNH_2$ in DMF. The configuration of compound (*S*)-(**Id**) first of all simply follows from the succession (*S*)-(**IV**) → (*S*)-(**VId**) → (4*R*)-(**VIId**) → (*S*)-(**Id**). Besides the sign (–) of the specific rotation of our (*S*)-**Id** sample coincides with the sign of (–)-**Id**, that has been obtained from the levorotatory alprenolol salt with L-(+)-tartaric acid [20]. In its turn salt **Id** was subjected to X-ray diffraction analysis [21], and the comparison of the relative alprenolol configuration in this crystal with the authentic configuration of the natural (*R*,*R*)-tartaric acid allowed assignment to alprenolol the configuration (*S*)-**Id**.

We can state in conclusion that we developed a working scheme of transition from the enantio-enriched glycidol through cyclic sulfites to various aryloxypropanolamines, in particular to β-adrenoblockaders. The choice of succession of the chemical operations is defined by the physico-chemical features of the initial hydroxyaromatic compound. In particular, with phenols possessing donor substituents a sequence "diol–sulfite" may be recommended, and for electron-deficient aryl- and hetarylhydroxides the substitution in chloromethylsulfites seems more preferable.*

* The authors are grateful to A. V. Pashagin who took part in carrying out some parts of the study.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometers Bruker WM-250, Gemini-200, and Varian T-60 at operating frequencies 250, 200, and 60 MHz respectively, internal reference TMS. ^{13}C NMR spectra were recorded on Bruker MSL 400 instrument at 100.6 MHz, solvent $CDCl_3$, as internal reference served the solvent peak (77.16 ppm). IR spectra were measured on spectrophotometer UR-20 from mulls in mineral oil. Melting point were determined on Boetius heating block. TLC was performed on Silufol plates. Optical rotation was measured on Polamat A polarimeter.

***rac*-3-Aryloxypropane-1,2-diols VI.** A mixture of 4 g (54 mmol) of glycidol, 0.5 g (5 mmol) of Et_3N, 54 mmol of an appropriate phenol, and 10 ml of anhydrous ethanol was refluxed for 2–4 h. On cooling the separated crystals of diols **VIb, c, f–j, l** were filtered off and recrystallized from ethanol. Diols **VIa, d, e, k, m–o** were isolated by vacuum distillation. Diols **VIa, e, m–o** crystallized on standing. The yields, boiling and melting points of the racemic diols are listed in Table 1. For enantioenriched diols prepared in a similar way the melting temperature and optical rotation are presented in Table 2.

(*S*)-3-(1-Naphthyloxy)propane-1,2-diol (*S*)-(VIb) was obtained similarly using (*S*)-glycidol of *ee* 90%, reaction time 1 h, the substance crystallized as soon as the reaction mixture cooled. IR spectrum, ν, cm^{-1}: 3300, 3220 (OH), 3060 (H arom), 1620, 1590, 1580, 1510 (Ar). ^{1}H NMR spectrum (60 MHz), δ, ppm (*J*, Hz): 2.63 br.s (2H, HO), 3.88 d (2H, CH_2O, 6.0), 4.16–4.33 m (3H, CHO, CH_2O); 6.88 d.d (1H, 7.0, 3.0), 7.16–7.57 m (4H), 7.66–7.93 m (1H), 8.05–8.26 m (1H) (all naphthyl) ^{13}C NMR spectrum, δ, ppm: 63.77 (CH_2OH), 69.28 (OCH_2), 70.56 (CH); 105.09, 120.84, 121.52, 125.26, 125.46, 125.65, 126.37, 127.49, 134.48, 154.04 (naphthyl). (Cf. spectral data in [19]).

(*S*)-3-[4-(*N*-Morpholino)-1,2,5-thiadiazolyloxy]-propane-1,2-diol (*S*)-(VIc). A mixture of 1.3 g (17 mmol) of (*S*)-glycidol of *ee* 90%, 0.5 g of Et_3N, 3.1 g (12 mmol) of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole, and 10 ml of ethanol was heated at reflux for 8 h. On completion of the reaction the mixture was cooled, the ethanol was distilled off. The brown substance obtained was ground in succession with dichloromethane and carbon tetrachloride, and the separated precipitate was recrystallized from ethanol to afford colorless crystals of propanediol (*S*)-**VIc**. IR spectrum, ν, cm^{-1}: 3400, 3270 (OH), 1540 (thiadiazole). ^{1}H NMR spectrum (60 MHz), δ, ppm (*J*, Hz): 2.82 br.s (2H, OH), 3.27–3.90 m (10H, CH_2 morph, OCH_2), 3.90–4.22 m (1H, OCH), 4.43 d (2H, OCH_2, 5.0). ^{13}C NMR spectrum, δ, ppm: 47.40 (CH_2N), 62.42 (CH_2OH), 65.63 (CH_2O morph), 69.33 (CH_2O), 71.41 (CHO), 149.88 (=C–N), 153.70 (=C–OCH_2).

(*S*)-3-(2-Allenylphenoxy)propane-1,2-diol (*S*)-(VId) was obtained in the same way as diol *rac*-**VId** using (*S*)-glycidol of *ee* 90%. IR spectrum, ν, cm^{-1}: 3400 (OH), 1645 (C=C), 1595, 1560, 1510 (Ar). ^{1}H NMR spectrum (200 MHz), δ, ppm (*J*, Hz): 3.15 br.s (2H, OH), 3.40 d (2H, –CH_2Ar, 6.0), 3.68–3.85 m and 3.95–4.15 m (together 5H, CHO, CH_2OH), 4.85 d (16.8) and 4.87 d (9.4) (together 2H, =CH_2), 5.69–5.93 m (1H, =CH), 6.60–7.08 m (4H, H arom). ^{13}C NMR spectrum, δ, ppm: 34.58 (CH_2–CH=), 63.87 (OCH_2), 69.38 (OCH_2), 70.78 (CH), 111.82 (CH=CH_2), 115.30 (CH=CH_2), 121.27 (C_{Ar}–H), 127.54 (C_{Ar}–H), 128.73 (*iso*-$C_{Ar}O$), 130.20 (C_{Ar}–H), 137.27 (C_{Ar}–H), 156.34 (*iso*-C_{Ar}–O).

4-Aryloxymethyl-1,3,2-dioxathiolane 2-oxides. Method A. 4-(2-Allyphenoxymethyl)-1,3,2-dioxathiolane 2-oxide (**VIId**). To a suspension of 0.24 g (10 mmol) of sodium hydride in 2 ml of toluene was added at room temperature while stirring a solution of 1.34 g (10 mmol) of *o*-allylphenol in 2 ml of toluene. The mixture was boiled for 30 min, and to the formed colorless paste was added a solution of 1.66 g (10 mmol) of diastereomer mixture of 4-chloromethyl-1,3,2-dioxathiolane 2-oxide (**V**) in 5 ml of toluene. Then the mixture was stirred at heating for 1 h. The separated precipitate was filtered off, the solvent from filtrate was distilled off, and the residue was vacuum-distilled. We isolated 0.8 g of 4-(2-allylphenoxymethyl)-1,3,2-dioxathiolane 2-oxide (**VIId**) as a mixture of *cis*- and *trans*-isomers, bp 123–127°C (0.05 mm Hg). IR spectrum, ν, cm^{-1}: 1645 (C=C), 1595 (Ar), 980, 1060 (C–O, S–O), 1220 (S=O). ^{1}H NMR spectrum (200 MHz), δ, ppm (*J*, Hz): 3.41 br.d (2H, CH_2Ar, 6.4); 3.93–4.15 m, 4.25–4.45 m, 4.49–4.58 m and 4.62–4.93 m [together 4.4H, OCH_2 (*cis*,*trans*), OCH (*cis*)]; 5.01–5.19 m (2H, =CH_2), 5.22–5.35 m [0.6H, CHO (*trans*)], 5.90–6.11 m (1H, CH=); 6.82–6.90 m (H arom), 6.92–7.05 m (1H, H arom) and 7.20–7.32 m (2H, H arom). ^{13}C NMR spectrum, δ, ppm: 33.85 and 33.87 (CH_2), 66.19 [CH_2O (*cis*)], 67.37 [CH_2O (*cis*)], 68.21 [CH_2O (*trans*)], 68.88 [CH_2O (*trans*)], 77.79 [CHO (*trans*)], 79.82 [CHO (*cis*)], 110.95 and 111.11 (CH=), 115.05 and 115.10 (=CH_2), 121.21 and 121.24, 127.06 and 127.07, 128.39 and 128.40, 129.79 and 129.83, 138.36 and 138.47, 155.17 and 155.18 (Ar).

Method B. (4*R*)-4-(2-Allyphenoxymethyl)-1,3,2-dioxathiolane 2-oxide (4*R*)-(**VIId**). To a stirred solution of 2.08 g (10 mmol) of (*S*)-3-(2-allylphenoxy)-propane-1,2,-diol (*S*)-(**VId**) in 10 ml of dichloromethane was added within 15 min dropwise at −20°C 1.19 g (10 mmol) of thionyl chloride in 5 ml of dichloromethane. The stirring was continued for 1 h, then the solvent was distilled off; an isomeric mixture of (*R*)-4-(2-allyphenoxymethyl)-1,3,2-dioxathiolane 2-oxides (**VIId**) was obtained in quantitative yield.

(4*R*)-4-[(4-Morpholino-1,2,5-thiadiazol-3-yl)oxymethyl]-1,3,2-dioxathiolane 2-oxides (4*R*)-(VIIc) were prepared similarly to sulfites (4*R*)-**VIId** along method B using 2 equiv of triethylamine for binding HCl. Yield 75%. The spectral characteristics are the same as published in [14].

(4*R*)-4-Naphthyloxymethyl-1,3,2-dioxathiolane 2-oxides (4*R*)-(VIIb) were prepared as a mixture of diastereomers similarly to sulfites (4*R*)-**VIId** along method B in quantitative yield. The spectra pattern is identical to superimposed spectra of individual isomers published in [14].

***trans*-4-(4-bromophenyloxymethyl)-1,3,2-dioxathiolane 2-oxides (*trans*)-(VIIh)** were prepared similarly from *rac*-3-(4-bromophenyloxy)propane-1,2-diol (**VIh**) and thionyl chloride along method B. From the reaction mixture separated the trans-diastereomer (yield 78%0, mp 100–101°C. IR spectrum, ν, cm^{-1}: 1595 (Ar), 975, 1050 (C–O, S–O), 1227 (S=O). ^{13}C NMR spectrum, δ, ppm: 66.90 (OCH_2), 68.72 (OCH_2), 77.76 (CH); 114.20, 116.55, 132.58, 157.13 (Ar).

(*S*)-1-(2-(Allylphenoxy)-3-isopropylamino-2-propanol [(*S*)-alprenol (*S*)-(Id)]. A mixture of 0.4 g (0.075 mmol) of dioxathiolanes (4*R*)-**VIId**, 1.6 g (27 mmol) of *i*-$PrNH_2$, and 6 ml of DMF was heated to 60–70°C for ~45 h. On completion of reaction the mixture was washed with 20 ml of 1 N NaOH water solution, and the product was extracted into ethyl acetate (3 × 60 ml). The extract was dried with $MgSO_4$, the solvent was removed in a vacuum. (*S*)-alprenol was isolated as a base, $[\alpha]_D^{20}$ −14.1 (*c* 3.8, EtOH) {publ.: $[\alpha]_D^{20}$ −15.2 (4%, EtOH) [20]}.

(*S*)-3-Isopropylamino-1-(naphthyl-1-oxy)-2-propanol [(*S*)-propanolol (*S*)-(Ib)] was prepared in a similar way. The residue after removing ethyl acetate was dissolved in ether, and dry HCl was passed through the solution. The precipitate was filtered off. We isolated (S)-propanolol hydrochloride in 80% yield, mp 193–194°C. $[\alpha]_D^{20}$ −24.5 (*c* 1.0, EtOH) {publ.: mp 194–196°C, $[\alpha]_D^{20}$ −25.1 (*c* 1.05, EtOH) [25]}.

(*S*)-1-(tert-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol [(*S*)-thymolol (*S*)-(Ic)] was synthesized similarly from dioxathiolanes (4*R*)-(**VIIc**) and *t*-$BuNH_2$. The reaction product was characterized as hemimaleate, yield 85%, mp 197–198°C (from ethanol), $[\alpha]_D^{20}$ −7.0 (*c* 5, 1 N HCl) {publ.: mp 198–199°C, $[\alpha]_D^{20}$ −7.5 (*c* 20, 1 N HCl) [26]}.

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