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A NEW ROUTE FOR THE SYNTHESIS OF 3-(3-THIENYLOXY)-1,2-PROPANEDIOLS AND 3-(3-THIENYLOXY)-1,2-EPOXYPROPANES

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**A NEW ROUTE FOR THE SYNTHESIS OF 3-(3-THIENYLOXY)-
1,2-PROPANEDIOLS AND 3-(3-THIENYLOXY)-1,2-EPOXYPROPANES**

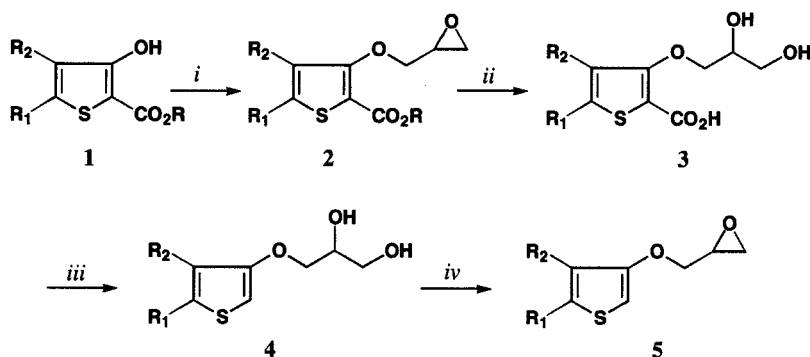
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The title compounds (**4** and **5**) are valuable intermediates for the preparation of diverse 3-thienyloxypropanolamines, which have shown different interesting pharmacological profiles.¹⁻⁷ Two possible routes start either from the bromo or the hydroxythiophene derivatives. In the first case, the key step is the substitution of the bromine atom of the appropriate bromothiophene by the 1,2-*O*-isopropylidenglyceryl group which could subsequently be transformed to the title compounds. However, in addition to the difficulty in obtaining the starting bromothiophene,⁸ this method is limited by the fact that the bromothiophenes bearing electron-withdrawing substituents cannot be used.⁹ On the other hand, the direct alkylation which is possible in benzene derivatives is limited by the fact that 3-hydroxythiophenes without electron-withdrawing groups are unstable, prone to air oxidation and difficult to obtain. These facts encouraged us to seek a different route which we now describe as a new and general method for the synthesis of 3-(3-thienyloxy)-1,2-propanediols (**4**) and 3-(3-thienyloxy)-1,2-epoxypropanes (**5**).

The starting air-stable hydroxythiophene derivatives **1**, may be synthesized generally in very good yields by the Fiesselmann procedure or its adaptation for the synthesis of condensed derivatives.¹⁰ The selective *O*-alkylation of these hydroxy compounds (**1**), was carried out by two procedures (Table 1). The first employed^{1,11} epichlorohydrin and potassium *t*-butoxide in dimethyl sulfoxide while the second one used ethyl methyl ketone and potassium carbonate with epibromohydrin as the alkylating agent. This new method allows an easier and cleaner work up and the yields are generally higher than in the classical method, although the reaction time is longer. The varying results in the alkylations of compound **1** are probably the result of different mechanisms (S_N1 vs S_N2) which are determined by the substituents on the thiophene ring, the solvent/base system and the alkylating agent used.

Compounds **2** were hydrolyzed completely to **3** by brief treatment (5-20 min) with sodium hydroxide and were isolated by acidification with a 5% aqueous hydrogen chloride solution (Table 2). The selective hydrolysis of the alkoxycarbonyl group could not be achieved under several different conditions. Compounds **3** underwent facile thermal decarboxylation upon heating in a Kugelrohr



- a) $\text{R} = \text{Me}$, $\text{R}_1 = \text{R}_2 = \text{H}$; b) $\text{R} = \text{R}_2 = \text{Me}$, $\text{R}_1 = \text{H}$; c) $\text{R} = \text{Me}$, $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{Ph}$;
 d) $\text{R} = \text{Me}$, $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{Cl}$; e) $\text{R} = \text{R}_1 = \text{R}_2 = \text{Me}$; f) $\text{R} = \text{Me}$, $\text{R}_1 = \text{R}_2 = \text{Cl}$;
 g) $\text{R} = \text{R}_2 = \text{Me}$, $\text{R}_1 = \text{Cl}$; h) $\text{R} = \text{Et}$, $\text{R}_1, \text{R}_2 = -(\text{CH}_2)_3-$; i) $\text{R} = \text{Et}$, $\text{R}_1, \text{R}_2 = -(\text{CH}_2)_4-$;
 j) $\text{R} = \text{Et}$, $\text{R}_1, \text{R}_2 = -(\text{CH}_2)_5-$; k) $\text{R} = \text{Et}$, $\text{R}_1, \text{R}_2 = -(\text{CH}_2)_6-$; l) $\text{R} = \text{Me}$, $\text{R}_1, \text{R}_2 = -\text{CH}(\text{Me})-(\text{CH}_2)_2-$;
 m) $\text{R} = \text{Me}$, $\text{R}_1, \text{R}_2 = -\text{CH}(\text{Me})-(\text{CH}_2)_3-$; n) $\text{R} = \text{Me}$, $\text{R}_1, \text{R}_2 = -(\text{CH}_2)_2-\text{CH}(\text{Me})-\text{CH}_2-$;
 o) $\text{R} = \text{Me}$, $\text{R}_1, \text{R}_2 = -(\text{CH}_2)_2\text{S}-$; p) $\text{R} = \text{Me}$, $\text{R}_1, \text{R}_2 = -(\text{CH}_2)_2-\text{S}-\text{CH}_2-$;
 q) $\text{R} = \text{Me}$, $\text{R}_1, \text{R}_2 = -(\text{CH}_2)_3\text{S}-$; r) $\text{R} = \text{Me}$, $\text{R}_1, \text{R}_2 = -\text{SCH} = \text{C}(\text{Me})$.

(i) Method A: Epichlorohydrin, *t*-BuOK, DMSO. Method B: Epibromohydrin, K_2CO_3 , ethylmethylketone. (ii) NaOH 1N, Δ (5-20 min), HCl 5%. (iii) Δ (20 min-3 hrs). (iv) 1: ClTs, Pyridine, H_2SO_4 dil. 2: NaOH 20%, 30 min r.t., DMSO.

SCHEME

apparatus or in a sublimation apparatus under reduced pressure (0.1 Torr.) approximately 30° above their melting points to afford good yields of diols **4** (Table 3). The only cases in which the yield was lower were those of the 4-chloro derivative **4d** and the 4,5-dichloro derivative **4b**, which was caused by the formation of the corresponding lactone derived from **3'** by an intramolecular cyclization favored by the presence of the chloro substituents.

The transformation of diols **4** to epoxy derivative **5** was carried out by treatment with *p*-toluenesulfonyl chloride in anhydrous pyridine followed by treatment of the crude reaction mixture (two regioisomers), with sodium hydroxide in dimethyl sulfoxide to yield **5**, which were purified by flash column chromatography (Table 4). The structure of all the new compounds was established on the basis of their analytical and spectroscopic data (Tables 1-4).

EXPERIMENTAL SECTION

Melting points were measured on a Buchi 510 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu-435 IR spectrophotometer and ^1H NMR on a Bruker AM (200 MHz) spectrometer. All the reagents used were of commercial grade and used as such. TLC plates and silica gel (230-240 mesh) were from E. Merck, Darmstadt. Microanalyses were performed on a Perkin-Elmer 240 analyzer.

The starting compounds **1** were prepared according to the literature: **1a**,¹² **1b,g**,¹³ **1c**,¹⁴ **1d**,¹⁵ **1e,h,i**,¹⁶ **1f**,¹⁷ **1j-q**,¹⁰ and **1r**.¹⁸

TABLE 1. Yields and Spectral Data of Compounds 2

Product	Yield (%) ^a		mp. (°C) (solvent) or bp. (°C) (Torr.)	IR ν (cm ⁻¹) CO	¹ H NMR (CDCl ₃ /TMS) ^b δ , <i>J</i> (Hz)
	A	B			
2a	67	60	70-71 (Pr ⁱ OH)	1695	6.88 (d, 1H, <i>J</i> = 5.5, H4 thiophene), 7.40 (d, 1H, <i>J</i> = 5.5, H-5 thiophene)
2b	—	79	158 (25)	1705	2.05 (s, 3H, CH ₃), 7.00 (s, 1H, H-5 thiophene)
2c	—	82	75-77 (Pr ⁱ OH)	1700	7.12-7.55 (m, 6H, aromatic protons)
2d	38	—	52-53 (Pr ⁱ OH)	1750	7.40 (s, 1H, H-5 thiophene)
2e	65	77	56-57 (Pr ⁱ OH)	1710	2.05 (s, 3H, 4-CH ₃), 2.32 (s, 3H, 5-CH ₃)
2f	50	—	78-79 (Pr ⁱ OH)	1710	—
2g	—	57	61-63 (benzene)	1715	2.02 (s, 3H, CH ₃)
2h	80	87	58-59 (Pr ⁱ OH)	1700	—
2i	84	66	50 (Pr ⁱ OH)	1700	—
2j	—	96	53-55 (Pr ⁱ OH)	1700	—
2k	—	91	oil	1705	—
2l	68	—	oil	1705	1.70 (d, 3H, <i>J</i> = 6.83, CH ₃)
2m	82	—	oil	1710	1.22 (d, 3H, <i>J</i> = 6.90, CH ₃)
2n	81	—	80-82 (Pr ⁱ OH)	1705	1.12 (d, 3H, <i>J</i> = 5.90, CH ₃)
2o	68	79	64-66 (MeOH)	1705	—
2p	—	47	oil	1710	—
2q	77	98	54-56 (Pr ⁱ OH)	1705	—
2r	42	—	122-123 (MeOH)	1700	2.47 (s, 3H, CH ₃), 6.92 (s, 1H thiophene)

a) Yields based on crystallized product. b) The compounds showed the expected ¹H NMR data for the methylene, methyne, oxymethylene, alkoxy and epoxy groups protons.

TABLE 2. Yields and Spectral Data of Compounds 3

Product	Yield (%) ^a	mp. (°C) ^b	IR ν (cm ⁻¹)		¹ H NMR (DMSO-d ₆ , TMS) ^c δ , <i>J</i> (Hz)
			CO	OH	
3a	60	122-123	1660	3250-3350	7.07 (d, 1H, <i>J</i> = 5.58, H-4 thiophene), 7.73 (d, 1H, <i>J</i> = 5.58, H-5 thiophene)
3b	74	120-121	1660	3250	1.82 (s, 3H, CH ₃), 7.12 (s, 1H, H-5 thiophene)
3c	72	117-118	1675	3300	7.00-7.35 (m, 5H, phenyl), 7.50 (s, 1H, H-5 thiophene)
3d	86	115-116	1685	3200-3400	7.87 (s, 1H, H-5 thiophene),
3e	87	125-126	1665	3250	2.25 (s, 3H, 4-CH ₃), 2.42 (s, 3H, 5-CH ₃)
3f	87	132-134	1685	3100-3200	—
3g	80	146-147	1635	3250-3400	1.90 (s, 3H, CH ₃)
3h	69	148-150	1670	3250	—
3i	52	133-135	1670	3320	—
3j	56	138-140	1680	3250-3360	—
3k	50	132-134	1690	3240-3385	—
3l	82	132-134	1680	3375	1.12 (d, 3H, <i>J</i> = 5.9, CH ₃)
3m	80	140-141	1670	3225-3350	1.17 (d, 3H, <i>J</i> = 6.9, CH ₃)
3n	60	142-143	1675	3100-3300	0.95 (d, 3H, <i>J</i> = 5.3, CH ₃)
3o	55	130-132	1680	3140-3360	—
3p	66	125-127	1690	3350	—
3q	82	112-114	1685	3260-3400	—
3r	84	141-142	1675	3200-3300	2.30 (s, 3H, CH ₃), 7.20 (s, 1H, thiophene)

a) Yields based on crystallized product. b) Recrystallized from EtOAc. c) The compounds showed the expected ¹H NMR data for the methylene, methyne, oxymethylene and hydroxy protons.

Alkyl 3-(2,3-Epoxy)propoxythiophene-2-carboxylates (2). General Procedures.

Method A.- Epichlorohydrin (2.3 g, 0.024 mol) was added dropwise to a stirred solution of the corresponding alkyl 3-hydroxythiophene-2-carboxylate (**1a-r**, 0.01 mol), *t*-BuOK (1.4 g, 0.012 mol) in DMSO (17 mL). The reaction mixture was heated at 100° for 2-3 hrs and after cooling to r.t. the solvent was distilled at 0.1 Torr. The residue was extracted with hot *n*-hexane, the solvent evaporated and the epoxy derivatives **2** formed were purified by crystallization or chromatography on a silica gel column using *n*-hexane/EtOAc (5:1) as eluent (Table 1).

Method B.- Anhydrous K₂CO₃ (1.4 g, 0.01 mol) was added to a stirred solution of the corresponding alkyl 3-hydroxythiophene-2-carboxylate (0.01 mol) in ethyl methyl ketone (30 mL) and stirring was continued for 10 min. Then epibromohydrin (1.9 g, 0.013 mol) was added and the mixture was heated at reflux for 2 days. The solvent was evaporated, cold water (20 mL) was added and the mixture was

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TABLE 3. Yields and Spectral Data of Compounds 4

Product	Yield ^a (%)	Heating time (min or hrs)	mp. (°C) (solvent)	IR ν (cm ⁻¹) OH	¹ H NMR (DMSO-d ₆ or CDCl ₃ , TMS) δ , <i>J</i> (Hz) ^b
4a	85	15 min ^c	65-67 ^d (benzene)	3200-3275	6.53 (dd, 1H, <i>J</i> = 3.14; 1.61, H-2 thiophene), 6.76 (dd, 1H, <i>J</i> = 5.23; 1.61, H-4 thiophene), 7.39 (dd, 1H, <i>J</i> = 5.23; 1.61, H-5 thiophene) ^e
4b	83	15 min ^c	74-76 ^f (EtOAc)	3100-3250	2.10 (s, 3H, CH ₃), 6.52 (d, 1H, <i>J</i> = 2.9, H-2 thiophene), 7.12 (d, 1H, <i>J</i> = 2.9, H-5 thiophene) ^e
4c	92	15 min ^c	46-47 (chloroform)	3250-3400	6.47 (d, 1H, <i>J</i> = 4.5, H-4 thiophene), 7.30-7.67 (m, 6H, aromatic protons) ^g
4d	28	20 min ^c	oil	3300-3400	6.30 (d, 1H, <i>J</i> = 2.9, H-2 thiophene), 7.05 (d, 1H, <i>J</i> = 2.9, H-5 thiophene) ^g
4e	85	10 min ^c	88-89 (EtOAc)	3250-3300	2.17 (s, 3H, 4-CH ₃), 2.35 (s, 3H, 5-CH ₃), 6.12 (s, 1H, H-2 thiophene) ^e
4f	39	20 min ^c	79-81 (EtOAc)	3150-3250	6.80 (s, 1H, H-2 thiophene) ^e
4g	61	20 min ^c	73-75 (benzene)	3150-3275	1.80 (s, 3H, CH ₃); 6.25 (s, 1H, H-2 thiophene) ^g
4h	71	10 min ^c	83-85 (benzene)	3325-3400	6.80 (s, 1H, H-2 thiophene) ^e
4i	71	20 min ^c	92-94 (EtOAc/hexane)	3275-3350	6.30 (s, 1H, H-2 thiophene) ^e
4j	94	3 hrs ^h	102-104 (ethylacetate)	3250-3350	6.07 (s, 1H, H-2 thiophene) ^e
4k	98	3 hrs ^h	86-88 (ethylacetate)	3275-3350	6.12 (s, 1H, H-2 thiophene) ^e
4l	82	1 hr ^h	86-88 (ethylacetate)	3225-3300	6.22 (s, 1H, H-2 thiophene) ^e
4m	89	2 hrs ^h	118-120 (ethylacetate)	3200-3300	1.07 (s, 3H, <i>J</i> = 6.9, 6-CH ₃), 6.15 (s, 1H, H-2 thiophene) ^e
4n	70	4 hrs ^h	98-100 (ethylacetate)	3225-3325	1.19 (d, 3H, <i>J</i> = 6.43, 5-CH ₃), 6.31 (s, 1H, H-2 thiophene) ^e
4o	87	4 hrs ^h	82-84 (ethylacetate)	3200-3300	6.40 (s, 1H, H-2 thiophene) ^e
4p	70	3 hrs ^h	146-148 (ethylacetate)	3150-3300	6.27 (s, 1H, H-2 thiophene) ^e
4q	96	3 hrs ^h	80 (ethylacetate)	3200-3300	6.30 (s, 1H, H-2 thiophene) ^e
4r	72	20 min ^c	111-112 (benzene)	3225-3300	2.37 (s, 3H, CH ₃), 6.52 (s, 1H, H-2 thiophene), 7.07 (s, 1H, H-4 thiophene) ^e

a) Yields based on crystallized product. b) The compounds showed the expected ¹H NMR data for the methylene, methyne, oxymethylene or hydroxy protons. c) In a Kugelrohr apparatus. d) Lit.² mp. 65-66°. e) In DMSO-d₆. f) Lit.³ 74-76°. g) In CDCl₃. h) In a sublimation apparatus.

TABLE 4. Yields and Spectral Data of Compounds 5

Product ^a	Yield (%)	¹ H NMR (CDCl ₃ , TMS), δ J (Hz)
5a	57	2.73 (dd, 1H, <i>J</i> = 4.95, 2.64, CH-CH ₂), 2.91 (dd, 1H, <i>J</i> = 4.95, 4.13, CH-CH ₂), 3.28-3.36 (m, 1H, CH), 3.91 (dd, 1H, <i>J</i> = 11.05, 5.70, OCH ₂), 4.21 (dd, 1H, <i>J</i> = 11.05, 3.13, OCH ₂), 6.29 (dd, 1H, <i>J</i> = 3.11, 1.54, H-2 thiophene), 6.77 (dd, 1H, <i>J</i> = 5.18, 1.54, H-4 thiophene), 7.17 (dd, 1H, <i>J</i> = 5.18, 3.11, H-5 thiophene).
5b	75	2.07 (s, 3H, CH ₃), 2.65-2.90 (m, 2H, CH-CH ₂), 3.22-3.40 (m, 1H, CH), 3.85 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.15 (dd, 1H, <i>J</i> = 11.9, 2.0, OCH ₂), 6.15 (d, 1H, <i>J</i> = 2.9, H-2 thiophene), 6.77 (d, 1H, <i>J</i> = 2.9, H-5 thiophene).
5c	82	2.55 (dd, 1H, <i>J</i> = 5.9, 2.9, CH-CH ₂), 2.67 (t, 1H, <i>J</i> = 5.9, CH-CH ₂), 3.07-3.27 (m, 1H, CH), 3.80 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.10 (dd, 1H, <i>J</i> = 11.9, 2.9 OCH ₂), 6.20 (d, 1H, <i>J</i> = 2.9, H-2 thiophene), 7.05-7.52 (m, 6H, aromatic protons).
5d	46	2.70-2.97 (m, 2H, CH-CH ₂), 3.27-3.47 (m, 1H, CH), 4.02 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.30 (dd, 1H, <i>J</i> = 11.9, 4.5, OCH ₂), 6.10 (d, 1H, <i>J</i> = 2.9, H-2 thiophene), 6.83 (d, 1H, <i>J</i> = 2.9, H-5 thiophene).
5e	62	2.35 (s, 3H, 4-CH ₃), 2.50 (s, 3H, 5-CH ₃), 2.70-2.97 (m, 2H, CH-CH ₂), 3.30-3.47 (m, 1H, CH), 3.97 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.35 (dd, 1H, <i>J</i> = 11.9, 2.9, OCH ₂), 6.00 (s, 1H, H-2 thiophene).
5f	70	2.78-3.05 (m, 2H, CH-CH ₂), 3.35-3.59 (m, 1H, CH), 4.04 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.32 (dd, 1H, <i>J</i> = 11.9, 4.5, OCH ₂), 6.40 (s, 1H, H-2 thiophene).
5g	73	1.90 (s, 3H, CH ₃), 2.55-2.80 (m, 2H, CH-CH ₂), 3.10-3.30 (m, 1H, CH), 3.72 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.07 (ss, 1H, <i>J</i> = 11.9, 2.9, OCH ₂), 5.82 (s, 1H, H-2 thiophene).
5h	75	1.46-1.88 (m, 2H, cycle), 2.40-2.76 (m, 6H, CH-CH ₂ and 4H cycle), 3.06-3.26 (m, 1H, CH), 3.79 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.19 (dd, 1H, <i>J</i> = 11.9, 2.9, OCH ₂), 5.83 (s, 1H, H-2 thiophene).
5i	77	1.40-1.84 (m, 4H, cycle), 2.52-2.80 (m, 6H, CH-CH ₂ and 4H cycle), 3.08-3.32 (m, 1H, CH), 3.83 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂).
5j	80	1.50-1.82 (m, 6H, cycle), 2.40-2.80 (m, 6H, CH-CH ₂ and 4H, cycle), 3.12-3.40 (m, 1H, CH), 3.85 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.27 (dd, 1H, <i>J</i> = 11.9, 2.9, OCH ₂), 5.87 (s, 1H, H-2 thiophene).
5k	71	1.27-1.87 (m, 8H, cycle), 2.62-3.00 (m, 6H, CH-CH ₂ and 4H, cycle), 3.32-3.52 (m, 1H, CH), 4.00 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.30 (dd, 1H, <i>J</i> = 11.9, 2.9, OCH ₂), 6.10 (s, 1H, H-2 thiophene).
5l	72	1.75 (d, 3H, <i>J</i> = 6.80, CH ₃), 2.47-2.52 (m, 1H, cycle), 2.70-2.97 (m, 2H, CH-CH ₂), 3.17-3.45 (m, 4H, CH and 3H, cycle), 3.75 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.12 (dd, 1H, <i>J</i> = 11.9, 2.9, OCH ₂), 6.10 (s, 1H, H-2 thiophene).
5m	57	1.22 (d, 3H, <i>J</i> = 6.90, CH ₃), 1.23-1.44 (m, 1H, cycle), 1.50-1.73 (m, 1H, cycle), 2.44-2.52 (m, 2H, cycle), 2.77-2.85 (m, 5H, 3H, cycle and CH-CH ₂), 3.17-3.40 (m, 1H, CH), 3.92 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.35 (dd, 1H, <i>J</i> = 11.9, 2.9, OCH ₂), 5.87 (s, 1H, H-2 thiophene).

TABLE 4. Continued

Product ^a	Yield	
	(%)	¹ H NMR (CDCl ₃ , TMS), δ J (Hz)
5n	80	1.20 (d, 3H, <i>J</i> = 5.90, CH ₃), 1.87-2.00 (m, 1H, cycle), 2.50-2.90 (m, 7H, CH-CH ₂ and 5H cycle), 3.05-3.30 (m, 1H, cycle), 3.32-3.40 (m, 1H, CH), 3.95 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.15 (dd, 1H, <i>J</i> = 11.9, 2.9, OCH ₂), 6.17 (s, 1H, H-2 thiophene)
5o	77	2.70-2.97 (m, 2H, CH-CH ₂), 3.10-3.20 (m, 2H, cycle), 3.25-3.45 (m, 1H, CH), 3.72-3.82 (m, 2H, cycle), 3.95 (dd, 1H, <i>J</i> = 11.9, 4.5, OCH ₂), 4.22 (dd, 1H, <i>J</i> = 11.9, 2.9, OCH ₂), 6.20 (s, 1H, H-2 thiophene).
5p	30	2.67-2.90 (m, 6H, CH-CH ₂ and 4H cycle), 3.22-3.42 (m, 1H, CH), 3.57 (s, 2H, SCH ₂), 3.90 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.20 (dd, 1H, <i>J</i> = 11.9, 2.9, OCH ₂), 6.00 (s, 1H, H-2 thiophene).
5q	72	2.05-2.25 (m, 2H, cycle), 2.70-3.00 (m, 6H, CH-CH ₂ and 4H cycle), 3.17-3.40 (m, 1H, CH), 3.92 (dd, 1H, <i>J</i> = 11.9, 5.9 OCH ₂), 4.20 (dd, 1H, <i>J</i> = 11.9, 2.9, OCH ₂), 6.07 (s, 1H, H-2 thiophene).
5r	66	2.37 (s, 3H, CH ₃), 2.77-3.0 (m, 2H, CH-CH ₂), 3.32-3.50 (m, 1H, CH), 4.0 (dd, 1H, <i>J</i> = 11.9, 5.9, OCH ₂), 4.32 (dd, 1H, <i>J</i> = 11.9, 2.9, OCH ₂), 6.17 (s, 1H, H-2 thiophene), 7.82 (s, 1H, H-5 thiophene).

a) Oils.

extracted with EtOAc (25 mL) and dried (Na₂SO₄). The solvent was removed by distillation and the epoxy derivatives formed were purified as described in method A.

3-[3-(2-Carboxythienyloxy)-1,2-propanediols (3). General Procedure.- A suspension of the alkyl 3-(2,3-epoxy)propoxythiophene-2-carboxylate (**2a-r**, 0.01 mol) in aqueous 1N NaOH (15 mL) was refluxed until total dissolution. The mixture was then acidified, with an aqueous 5% HCl solution (with cooling to 0°) to pH 1 and was extracted with EtOAc (25 mL). The organic layer was dried (Na₂SO₄), the solvent evaporated and the residue purified by crystallization from EtOAc.

3-(3-Thienyloxy)-1,2-propanediols (4). General Procedure.- Compounds **3** when heated at reduced pressure (0.1 Torr.) 30° above their melting points in a Kugelrohr or in a sublimation apparatus for the time listed in Table 3 yielded compounds **4** which were purified by crystallization.

3-(3-Thienyloxy)-1,2-epoxypropanes (5). General Procedure.- *p*-Toluene-sulfonyl chloride (1.9 g, 0.01 mol) was added at 0° to a stirred solution of the corresponding 3-(3-thienyloxy)-1,2-propanediol (**4a-r**, 0.01 mol) in anhydrous pyridine (22.5 mL). The reaction mixture was left for 1 day at r.t. and then, with cooling with an ice-bath a solution of H₂SO₄ (8.7 mL) in water (50 mL) was added. The organic layer was separated and the aqueous one was extracted with EtOAc (30 mL). The combined organic extracts were dried (Na₂SO₄) and evaporated at reduced pressure to afford the two possible monotosyl derivatives (two spots by tlc) as oils which were not purified.

The crude product was dissolved in DMSO (7.6 mL) and a 20% aqueous solution of sodium hydroxide (3.8 mL) was added. The reaction mixture was stirred for 30 min., whereupon water (7.6 mL) was added. The resulting solution was extracted with EtOAc (30 mL) and the organic extract was dried

(Na₂SO₄) and evaporated to dryness to yield compounds **5** as oils which were purified by chromatography on a silica gel column using (hexane/EtOAc) (10/1) as eluent (Table 4).

TABLE 5. Combustion Analysis Data of New Compounds

Cmpd	Calcd. (Found)				Cmpd	Calcd. (Found)			
	C	H	Cl	S		C	H	Cl	S
2a	50.47 (50.32)	4.71 (4.43)		14.97 (14.72)	4c	62.38 (62.57)	5.64 (5.34)		12.81 (12.97)
2b	52.61 (52.36)	5.30 (5.07)		14.04 (13.83)	4d	40.29 (40.57)	4.35 (4.52)	16.99 (16.92)	15.36 (15.23)
2c	62.06 (61.83)	4.86 (4.57)		11.04 (11.24)	4e	53.43 (53.62)	6.98 (6.87)		15.85 (16.07)
2d	43.47 (43.56)	3.65 (3.32)	14.25 (14.35)	12.89 (12.85)	4f	34.58 (34.47)	3.32 (3.52)	29.17 (29.28)	13.19 (12.83)
2e	54.53 (54.77)	5.82 (5.58)		13.23 (13.09)	4g	43.15 (43.24)	4.98 (4.72)	15.92 (15.82)	14.40 (14.57)
2f	38.18 (38.27)	2.85 (2.83)	25.05 (25.32)	11.32 (11.36)	4h	56.05 (56.32)	6.58 (6.71)		14.96 (15.02)
2g	45.72 (45.35)	4.22 (4.43)	13.50 (13.45)	12.20 (12.06)	4i	57.87 (57.62)	7.06 (6.90)		14.04 (14.27)
2h	58.20 (58.22)	5.96 (6.00)		11.95 (12.14)	4j	59.48 (59.38)	7.49 (7.23)		13.23 (13.48)
2i	59.54 (59.25)	6.42 (6.57)		11.35 (11.34)	4k	60.90 (60.73)	7.86 (7.57)		12.50 (12.21)
2j	60.78 (60.77)	6.80 (6.52)		10.82 (10.97)	4l	57.87 (57.62)	7.06 (7.10)		14.04 (14.25)
2k	61.91 (61.85)	7.14 (7.28)		10.33 (10.09)	4m	59.48 (59.25)	7.49 (7.41)		13.23 (13.31)
2l	58.20 (58.22)	6.01 (6.00)		11.95 (12.14)	4n	59.48 (59.20)	7.49 (7.45)		13.23 (13.30)
2m	59.54 (59.25)	6.43 (6.57)		11.35 (11.34)	4o	46.53 (46.43)	5.21 (4.92)		27.60 (27.43)
2n	59.54 (59.25)	6.43 (6.43)		11.35 (11.13)	4p	48.77 (48.53)	5.73 (5.40)		26.03 (26.27)
2o	48.52 (48.63)	4.44 (4.27)		23.55 (23.78)	4q	48.77 (48.53)	5.73 (5.72)		26.03 (26.24)
2p	50.35 (50.47)	4.93 (4.72)		22.39 (22.35)	4r	49.16 (49.32)	4.95 (4.68)		26.25 (26.38)
2q	51.98 (52.28)	5.37 (5.42)		21.34 (21.44)	5c	67.22 (67.41)	5.21 (5.36)		13.80 (13.73)

3-(3-THIENYLOXY)-1,2-PROPANEDIOLS AND 3-(3-THIENYLOXY)-1,2-EPOXYPROPANES

TABLE 5. Continued

Cmpd	Calcd. (Found)				Cmpd	Calcd. (Found)			
	C	H	Cl	S		C	H	Cl	S
2r	50.70 (50.86)	4.25 (4.13)		22.55 (22.35)	5d	44.11 (44.29)	3.70 (3.72)	19.12 (19.24)	16.82 (16.99)
3a	44.04 (44.32)	4.62 (4.38)		14.69 (14.50)	5e	58.69 (58.97)	6.57 (6.41)		17.40 (17.70)
3b	46.55 (46.37)	5.21 (5.23)		13.81 (13.58)	5f	37.35 (37.51)	2.69 (2.68)	31.50 (31.42)	14.24 (14.51)
3c	57.13 (57.26)	4.79 (4.52)		10.89 (10.77)	5g	46.94 (46.69)	4.43 (4.18)	17.32 (17.25)	15.66 (15.51)
3d	38.02 (38.32)	3.59 (3.43)	14.03 (14.26)	12.69 (12.52)	5h	61.19 (61.33)	6.16 (6.12)		16.33 (16.27)
3e	48.77 (48.65)	5.73 (5.56)		13.02 (12.87)	5i	62.82 (62.69)	6.71 (6.69)		15.24 (15.07)
3f	33.47 (33.25)	2.81 (2.59)	24.70 (24.53)	11.17 (10.92)	5j	64.26 (64.49)	7.19 (7.13)		14.29 (14.48)
3g	40.53 (40.55)	4.16 (4.39)	13.29 (13.38)	12.02 (12.31)	5k	65.52 (65.17)	7.61 (7.48)		13.45 (13.31)
3h	51.15 (50.96)	5.46 (5.32)		12.41 (12.27)	5l	62.82 (62.75)	6.71 (6.59)		15.24 (15.47)
3i	52.93 (52.75)	5.92 (5.62)		11.77 (11.92)	5m	64.26 (64.51)	7.19 (7.14)		14.29 (14.46)
3j	54.54 (54.25)	6.34 (6.42)		11.20 (11.39)	5n	64.26 (63.99)	7.19 (7.13)		14.29 (14.42)
3k	55.98 (56.29)	6.71 (6.58)		10.67 (10.38)	5o	50.44 (50.69)	4.70 (4.51)		29.92 (29.77)
3l	52.93 (52.71)	5.92 (5.88)		11.77 (12.02)	5p	52.61 (52.51)	5.30 (5.23)		28.09 (27.90)
3m	54.54 (54.27)	6.34 (6.35)		11.20 (11.40)	5q	52.61 (52.47)	5.30 (5.21)		28.09 (28.32)
3n	54.54 (54.74)	6.34 (6.35)		11.20 (11.29)	5r	53.08 (52.79)	4.45 (4.53)		28.33 (28.10)
3o	43.47 (43.38)	4.38 (4.52)		23.21 (23.50)					
3p	45.51 (45.32)	4.86 (4.77)		22.08 (22.32)					
3q	45.51 (45.27)	4.86 (4.58)		22.08 (22.25)					
3r	45.83 (45.56)	4.19 (4.27)		22.24 (22.35)					

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