β-Adrenoceptor Studies. 2. Effects of Alkyl Substitution on β-Adrenoceptor Blocking, Antiarrhythmic, and Local Anesthetic Activities of 1,1'-(o-Phenylenedioxy)bis(3-isopropylamino-2-propanol)

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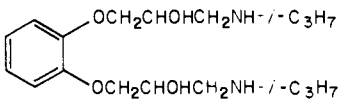
A series of bis(2-hydroxy-3-isopropylaminopropyl) ethers of nuclear-substituted catechols (1–7) has been synthesized and examined in vitro for β-adrenoceptor blocking activity, antagonism of ouabain-induced arrhythmias, and local anesthetic activity. Both tracheal and right atrial β-adrenoceptor blocking activity are markedly decreased by alkyl substitution in position 3 of parent catechol diether 1. Substitution in position 4 still lowers the affinity to cardiac β-adrenoceptors whereas the potency on tracheal receptors is only marginally changed. Antagonism to ouabain-induced arrhythmias and local anesthetic activity increases with introduction of alkyl substituents in the 3 as well as in the 4 position. In contrast with biological activities, the partition coefficient 1-octanol–phosphate buffer, pH 7.40, of 1 did not change significantly by 3- and 4-methyl substitution. Stepwise multiple regression analyses were performed using log P or π values in combination with $pK_{a(m)}$, E_s, or σ. With cardiac β-adrenoceptor blocking activity the optimal equation contained E_s and π parameters, tracheal activity appeared to depend mainly on the E_s parameter, whereas for antiarrhythmic and local anesthetic activities the lipophilicity of the substituents appeared to be the determinant factor.

In our previous paper[1] we described the synthesis and biological properties of a series of bis(2-hydroxy-3-isopropylaminopropyl) ethers of dihydroxybenzenes, dihydroxynaphthalenes, and 2,2'-dihydroxybiphenyl. Among the phenyl diethers, ortho diether 1 appeared to have a much higher β-adrenoceptor blocking activity both on right atrial and on tracheal preparations of the guinea pig than its meta and para isomers. The same observation was



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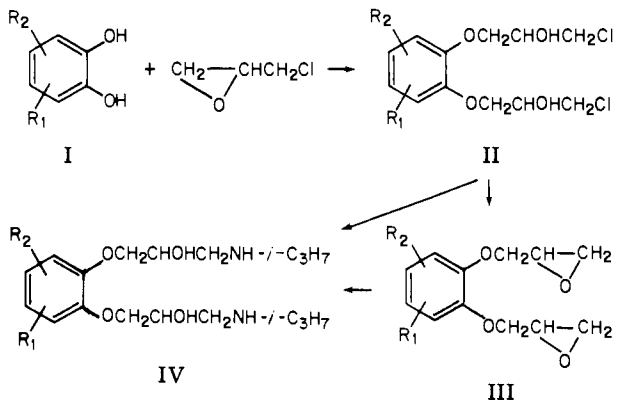
made with respect to the antagonistic potencies against ouabain-induced arrhythmias in the guinea pig right atrium. In contrast, the local anesthetic activities by these three diethers, measured on the isolated frog sciatic nerve, were of a similar low level.

Although the structure–activity relationships found with the six naphthyl diethers confirmed that β-adrenoceptor blockade does not contribute to antagonism of ouabain-induced arrhythmias in vitro, the particular position of ortho compound 1 regarding the β-adrenoceptor blocking and nonspecific antiarrhythmic activities induced us to prepare a series of diethers of nuclear-substituted catechols.

Chemistry. The compounds were prepared by amination of the appropriate bis(3-chloro-2-hydroxypropyl) ethers II either directly or after conversion into bis(2,3-epoxypropyl) ethers III (Scheme I).

Intermediates II were obtained by reaction of catechols I with 4 equiv of epichlorohydrin and catalytic amounts of NaOH at 40 °C. TLC analyses of the reaction mixtures revealed that at this temperature the formation of 2-hydroxymethyl-1,4-benzodioxanes[2] was still virtually absent with a 4-substituted, a 4,5-disubstituted, and the unsubstituted catechol as the starting products. With the 3-alkylcatechols as reactants even prolonged reaction times at 40 °C were by no means sufficient to etherify all OH groups, monoethers remaining present in the reaction mixtures. Higher reaction temperatures only improved the yields of the corresponding 2-hydroxymethyl-1,4-benzodioxanes, however. Prior to the reaction with isopropylamine, most of the II and III were partially purified by molecular distillation. On amination of the molecular distilled II of 3-methylcatechol and 3-isopropylcatechol,

Scheme I



the monoethers still present were virtually quantitatively converted into the corresponding benzodioxanes (see Experimental Section). Table I summarizes the synthetized bis(2-hydroxy-3-isopropylaminopropyl) ethers. ^1H NMR spectra were completely consistent with the assigned structures.

Apparent partition coefficients, 1-octanol–phosphate buffer, pH 7.40, and apparent dissociation constants of the diethers were determined and incorporated in a multiple regression analysis on the biological activities.

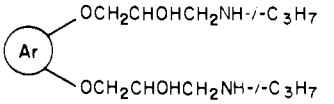
Pharmacology. β-Adrenoceptor blocking activity was estimated on the isolated right atrium and on the tracheal strip preparation of the guinea pig using isoprenaline as the agonist. Antagonism of ouabain-induced arrhythmias and inotropic and chronotropic effects, as caused by the minimal antiarrhythmic concentrations, were also determined on the guinea pig right atrium. Local anesthetic activity was measured on the isolated, partially desheathed sciatic nerve of the frog. Experimental details of all testing methods have been described in paper 1.[1]

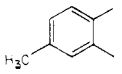
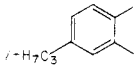
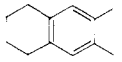
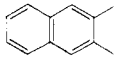
Results and Discussion

Table II summarizes the biological activities except for the inotropic and chronotropic effects which are depicted in Figure 1.

β-Adrenoceptor Blocking Activity. Introduction of alkyl groups into the 3 position of the phenyl nucleus of parent catechol diether 1 markedly lowers the affinity to the β-adrenoceptors. This decrease becomes more pronounced as the alkyl group increases in bulk and is ob-

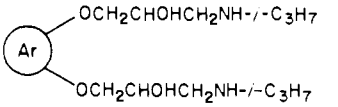
Table I. Preparative Data and Physical Properties

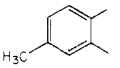
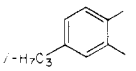
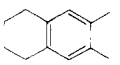
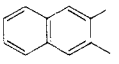


Compd	Ar	Mp, °C	Crystn solvent	Emp formula[a]	Yield, %
2		151-152	Me_2CO-EtOH	$C_{19}H_{34}N_2O_4 \cdot 2HCl$	43[b]
3		166-168	Me_2CO-EtOH	$C_{21}H_{38}N_2O_4 \cdot 2HCl$	26[b]
4		92.5-95	Me_2CO-EtOH	$C_{19}H_{34}N_2O_4 \cdot 2HCl$	63[b]
5		51-55	Me_2CO	$C_{21}H_{38}N_2O_4 \cdot 2HCl$	78[c]
6		73-74.5	Et_2O	$C_{22}H_{38}N_2O_4$	41[b]
7		198-202	Me_2CO-EtOH	$C_{22}H_{34}N_2O_4 \cdot 2HCl$	87[c]

[a] Base analyzed for C, H, and N; salts analyzed for C, H, N, and Cl. [b] Calculated with reference to dihydroxyarene. [c] Calculated with reference to bis(2,3-epoxypropyl) ether.

Table II. β-Adrenoceptor Blocking Activity on Guinea Pig Tracheal Strip and Right Atrium,[a] Activity against Ouabain-Induced Arrhythmias in Guinea Pig Right Atrium,[b] and Local Anesthetic Activity on the Partially Desheathed Frog Sciatic Nerve[c]



Compd	Ar	β-Adrenoceptor blocking action: pA_2 trachea	β-Adrenoceptor blocking action: pA_2 atrium	Antiarrhythmic act.	Local anesthetic act.
1[d]		6.73 ± 0.05 (18)	6.49 ± 0.07 (6)	3.70	1.29 ± 0.02
2		5.80 ± 0.08 (12)	5.48 ± 0.12 (7)	4.70	1.80 ± 0.02
3		5.35 ± 0.11 (5)	4.59 ± 0.13 (6)	5.00	2.00 ± 0.03
4		6.66 ± 0.09 (10)	6.22 ± 0.06 (6)	4.30	1.69 ± 0.03
5		6.48 ± 0.09 (8)	5.64 ± 0.15 (10)	4.70	2.07 ± 0.02
6		6.89 ± 0.06 (12)	5.83 ± 0.09 (8)	5.00	2.02 ± 0.03
7		6.80 ± 0.04 (11)	5.45 ± 0.15 (7)	5.30	2.20 ± 0.02

[a] pA_2 values ± SE, with the number of experiments in parentheses. [b] −Log minimal concentration (molar). [c] −Log EC_{50} (molar) ± SE; number of experiments, 10. [d] Taken from paper 1.[1]

served to a larger degree with atrial than with tracheal receptors; the 3-isopropyl compound **3** is about 30 and 80 times less active on trachea and atrium than **1**, respectively. Substitution at position 4 produces much less effect although a similar tendency is noticeable; while the differences between the activities of **1**, **4**, and **5** on the trachea are only marginal, the competitive antagonistic activities on the atrium of **4** and **5** show a two- and sevenfold decrease with respect to that of **1**, respectively. The activities of the 4,5-disubstituted diethers **6** and **7** are in line with the above observations.

Antiarrhythmic Activity. Quite opposite observations were made with the antagonistic potencies against ouabain-induced arrhythmias. Table II shows that alkyl

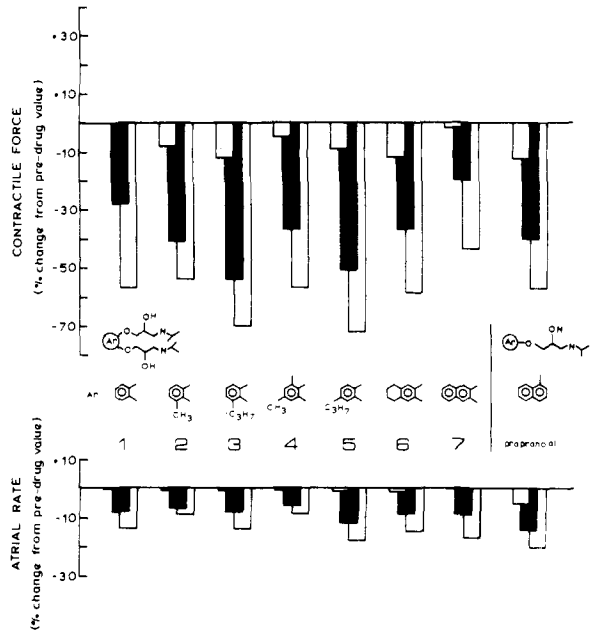


Figure 1. Inotropic and chronotropic effects on the isolated right atrium of the guinea pig. Each set of bars represents from left to right the changes after 1–2, 15, and 30 min of incubation with the compounds in their minimal antiarrhythmic concentrations.

substitution increases the potency and, again, substitution at position 3 has the stronger effect which becomes more pronounced as the alkyl group increases in size. Very pronounced potencies are likewise noted with **6** and **7**.

Inotropic and Chronotropic Effects. The changes in contractile force and rate during the 30-min incubation period of the minimal antiarrhythmic concentrations are depicted in Figure 1. All drugs are cardiodepressant. The negative chronotropic effects of the present diethers show some parallelism with the negative inotropic effects, which illustrates the well-known functional link between beat frequency and strength of myocardial contractions.[3] Interestingly, the 3- and 4-methyl-substituted and the 3- and 4-isopropyl-substituted diethers displayed similar effects, respectively. For comparison, the effects produced by propranolol are also included in the figure (cf. paper 1[1]). The moderate reduction of right atrial rate by the ortho diethers in their minimal antiarrhythmic concentrations suggests that this class of compounds, like propranolol, will only reduce the upstroke velocity of atrial action potentials which Vaughan Williams[4] denoted Class I of antiarrhythmic action.

Local Anesthetic Activity. As is the case with antiarrhythmic activity, the local anesthetic potencies also increase with introduction of alkyl substituents, the isopropyl group having a stronger effect than the methyl group. The potency levels of **6** and **7** are in line with the high antiarrhythmic activities.

Interrelationships. The effects of substitution on the antiarrhythmic (AA), local anesthetic (LA), and right atrial β-adrenoceptor blocking (β-A) activities are illustrated in Figure 2. Quite obviously, the AA activity pattern shows a parallelism to that of LA activities. As was the case with the phenyl, naphthyl, and biphenyl diethers reported previously,[1] differences in LA activities are less pronounced than the changes in AA activities. The highly significant regression equation connecting these activities is as follows

$$\mathrm{AA} = 1.661\ (7.34)\ \mathrm{LA} + 1.570 \qquad (1)$$
$$n = 7,\ r = 0.957,\ s = 0.170,\ p < 0.001$$

in which n represents the number of compounds, r the

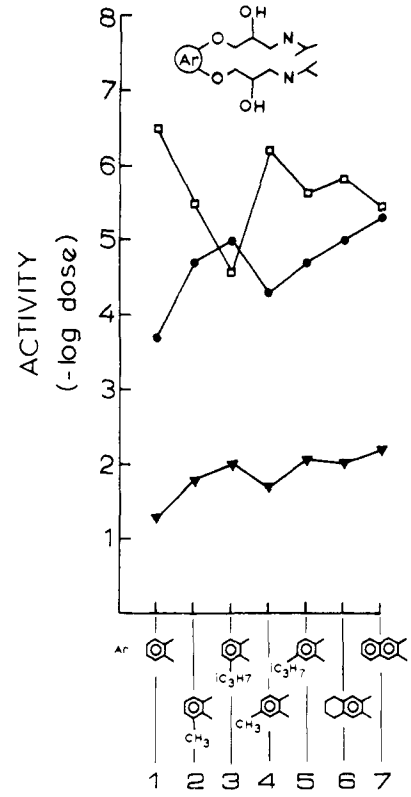


Figure 2. Pattern of pharmacological properties. Values taken from Table II: □-□, cardiac β-adrenoceptor blocking activity; ●-●, antagonism of ouabain-induced arrhythmias; ▼-▼, local anesthetic activity.

correlation coefficient, s the standard deviation, and p the level of significance as determined from the F value; the regression coefficient has its computed t value in parentheses. It should be noticed also that the distances between AA and LA activities of the present compounds are larger than those observed with the nonortho diethers reported previously.[1] This demonstrates that catechol diethers are indeed a separate class in having a higher selectivity to stabilize cardiac membranes.

The cardiac β-A activities show a pattern that is almost diametrically opposed to that of AA activities (Figure 2) which demonstrates the total absence of any contribution of β-adrenoceptor blockade to antagonism of ouabain-induced arrhythmias in vitro; the close relationship of the latter activity with LA activity confirms that this in vitro AA activity is only based on "membrane stabilizing" properties.

Multiple Regression Analysis (MRA). The clear-cut dependence of the specific β-A and the nonspecific AA and LA activities on the substitution pattern was analyzed more quantitatively by a MRA.

With regard to the dissociation constants and the partition coefficients, 1-octanol–phosphate buffer, pH 7.40, of the present ortho diethers, observations were made analogous to those reported previously with phenyl, naphthyl, and biphenyl diethers,[1] i.e., one point of neutralization despite the presence of two amino groups and very low partition coefficients, respectively. Table III shows only small differences among the acid dissociation constants and on the basis of the assumption that the $pK_{a(m)}$ values may be considered as the mean of $pK_{a(1)}$ and $pK_{a(2)}$ (cf. discussion in paper 1[1]) it can be calculated that for a compound with an average $pK_{a(m)}$ of 9.23, 97.11% is present in diprotonized form, 2.87% as monoprotonized, and only 0.021% as uncharged product at pH 7.40. These figures not only explain the very low partition coefficients

Table III. Physicochemical Parameters Used for Deriving Eq 2-8

Compd	Log P^a	$pK_{a(m)}{}^b$	π^c	$E_s{}^d$	σ^e
1	−1.187	9.22 ± 0.01	0	1.24	0
2	−1.174	9.23 ± 0.02	0.56	0	−0.13
3	−0.747	9.24 ± 0.04	1.53	−0.47	−0.23
4	−1.155	9.24 ± 0.02	0.56	1.24	−0.07
5	−0.833	9.30 ± 0.02	1.53	1.24	−0.07
6	−0.726	9.17 ± 0.03	1.39	1.24	−0.48
7	−0.810	9.18 ± 0.06	1.32	1.24	0.04

[a] Apparent partition coefficients, 1-octanol-phosphate buffer, pH 7.40; mean values of three experiments. [b] $pK_{a(m)}$ (see text) ± SE. [c] From Hansch et al.[7] [d] Steric factors for substituents in the 3 position; values taken from Taft.[8] [e] σ constants based upon position 2; hence, a group at position 3 is considered to exert an ortho σ effect; values taken from Charton[9] and from Hansch et al.[7]

Table IV. Observed and Calculated Biological Activities

	β-$A_{trachea}$		β-A_{atrium}		AA		LA	
Compd	Obsd	Calcd[a]	Obsd	Calcd[b]	Obsd	Calcd[c]	Obsd	Calcd[d]
1	6.73	6.72	6.49	6.51	3.70	3.64	1.29	1.27
2	5.80	5.76	5.48	5.46	4.70	4.58	1.80	1.77
3	5.35	5.38	4.59	4.60	5.00	4.95	2.00	2.06
4	6.66	6.66	6.22	6.17	4.30	4.58	1.69	1.77
5	6.48	6.48	5.64	5.58	4.70	4.95	2.07	2.06
6	6.89	6.87	5.83	5.66	5.00	4.99	2.02	2.07
7	6.80	6.84	5.45	5.71	5.30	5.00	2.20	2.06

[a] Equation 2. [b] Equation 4. [c] Equation 7. [d] Equation 8.

but also the fact that introduction of hydrophobic substituents in the phenyl ring of 1 does not (compounds 2 and 4), or significantly less than calculated, contribute to log P values. This is in contrast with the observations made by Hellenbrecht et al.[5] on a series of related 1-(alkylphenoxy)-3-isopropylamino-2-propanols in which the increase in log P values, 1-octanol–buffer, pH 7.0, caused by the alkyl substituents essentially obeyed the Hansch rules.

Since, on the other hand, the biological activities clearly depend on the position and size of the substituents, stepwise MRA's were performed not only with log P and $(\log P)^2$ but also with π and π^2 in combination with the $pK_{a(m)}$ values and the substituent constants E_s and σ. The independent variables used are listed in Table III. The squared correlation matrix showed the absence of collinearity between the variables used; naturally, any combination of log P and π parameters was excluded. The limited number of compounds induced us to accept not more than two different independent variables in the regression equation in order to minimalize the possibility of chance correlations.[6] The computations were performed on a CDC Cyber 73-28 computing system with multiple regression program REGRB2.

For tracheal β-A activities the most relevant equation was

$$\beta\text{-}A_{trachea} = 0.750\ (39.89)\ E_s - 2.961\ (9.28)\ pK_{a(m)} + 33.093 \quad (2)$$
$$n = 7,\ r = 0.999,\ s = 0.033,\ p < 0.001$$

Without the $pK_{a(m)}$ term the following relationship was found

$$\beta\text{-}A_{trachea} = 0.777\ (9.86)\ E_s + 5.751 \quad (3)$$
$$n = 7,\ r = 0.975,\ s = 0.141,\ p < 0.001$$

indicating, as expected, that the $pK_{a(m)}$ values have only minor, though statistically significant, relevance to this biological activity. The highly significant correlation with the E_s parameter is not surprising since Table II reveals that only substitution at the 3 position significantly lowers tracheal β-A activity.

With respect to the affinity to right atrial β-adrenoceptors, the most relevant equation was as follows

$$\beta\text{-}A_{atrium} = 0.571\ (6.39)\ E_s - 0.610\ (5.64)\ \pi + 5.804 \quad (4)$$
$$n = 7,\ r = 0.977,\ s = 0.159,\ p < 0.005$$

Here the following relationships with E_s and π separately were obtained

$$\beta\text{-}A_{atrium} = 0.648\ (2.74)\ E_s + 5.141 \quad (5)$$
$$n = 7,\ r = 0.775,\ s = 0.424,\ p < 0.05$$

and

$$\beta\text{-}A_{atrium} = -0.715\ (2.24)\ \pi + 6.375 \quad (6)$$
$$n = 7,\ r = 0.707,\ s = 0.475,\ p < 0.10$$

indicating that only the combination of the two parameters describes biological activity adequately.

The participation of the E_s parameter in the two optimal equations 2 and 4 suggests a low bulk tolerance to position 3 of the phenyl ring both with tracheal and cardiac β-adrenoceptors; the additional negative contribution of the π parameter in eq 4 might indicate the involvement of hydrophobic interactions with accessory areas which would disturb the interaction of the phenyl ring with the cardiac β-adrenoceptor. In spite of the fact that in vitro pA_2 values generally are considered to be proportional with receptor affinities, it should, however, be noted that the above conclusions are necessarily tentative and only restricted to the present class of diethers.

Both AA activity and LA activity appeared to correlate best with only the π parameter:

$$AA = 2.134\ (2.84)\ \pi - 0.836\ (1.90)\ \pi^2 + 3.644 \quad (7)$$
$$n = 7,\ r = 0.924,\ s = 0.249,\ p < 0.025$$

$$LA = 1.113\ (4.07)\ \pi - 0.389\ (2.42)\ \pi^2 + 1.271 \quad (8)$$
$$n = 7,\ r = 0.970,\ s = 0.091,\ p < 0.005$$

Introduction of a second parameter did not significantly further improve these relationships. These results clearly demonstrate the lipophilicity of the substituents to be the

determinant factor in AA and LA activities which, in turn, confirms the nonspecific character of both activities. Similar findings have been reported recently on related β-adrenoceptor blocking monoethers in relation to their in vivo and in vitro cardiodepressant activities.[5] Table IV compares the observed activities with those predicted by the optimal equations.

Experimental Section

Melting points were determined on a Reichert microscope with Kofler heating and are uncorrected. ^{1}H NMR spectra were recorded on a Varian A-60 instrument using $CDCl_3$ or D_2O as solvents and Me_4Si or sodium 3-(trimethylsilyl)propanesulfonate (TMSPS) as internal standards. Elemental analyses indicated were within ±0.4% of the theoretical values. All *o*-dihydroxyarenes were from commercial sources except for 2,3-dihydroxy-5,6,7,8-tetrahydronaphthalene which was prepared from veratrole according to Haworth and Mavin;[10] the final step, namely, demethylation of the methoxy groups, was accomplished in 96% yield by treatment with BBr_3 in CH_2Cl_2 according to McOmie et al.[11]

1,1′-(3-Methylphenylene-1,2-dioxy)bis(3-chloro-2-propanol) (2a). A solution of 12.4 g (0.1 mol) of 3-methylcatechol, 37.0 g (0.4 mol) of epichlorohydrin and 0.4 mL of 10 N NaOH was stirred under N_2 at 40 °C for 48 h. After evaporation of the epichlorohydrin in vacuo at 40 °C, the residual oil was taken up in $CHCl_3$, washed twice, and concentrated. Molecular distillation yielded 21.3 g of impure **2a**.

1,1′-(3-Methylphenylene-1,2-dioxy)bis(3-isopropylamino-2-propanol) (2). A solution of 13.1 g of impure **2a**, 14.8 g (0.25 mol) of *i*-$PrNH_2$, and 15.0 mL of C_6H_6 was heated in a Carius tube at 80 °C for 8 h. After concentration, the product was taken up in 4 N AcOH and extracted carefully with $CHCl_3$. The amino ether was liberated with 2 N NaOH, taken up in $CHCl_3$, washed, and concentrated to give 0.0252 mol of **2** in a purity of 99.6% (potentiometric titration): yield, as calculated with reference to 3-methylcatechol, 43%. The compound was taken up in anhydrous Et_2O and treated with the calculated amount of ethereal HCl solution to afford the dihydrochloride salt. On TLC (silica gel GF_{254}, 20 vol % Me_2CO in $CHCl_3$) of the original $CHCl_3$ extract only one spot appeared. GLC (20% SE-30 on Chromosorb W 60–80) confirmed[12] it to consist of a mixture of 2-hydroxymethyl-5- and -8-methylbenzodioxane. Single molecular distillation gave 0.0206 mol: n^{20}D 1.5510 (lit.[12] n^{25}D 1.5488 and 1.5510 for the 5-methyl and 8-methyl isomer, respectively); total yield of amino ether and benzodioxanes, 0.0458 mol. Anal. ($C_{10}H_{12}O_3$) C, H.

On amination of molecular distilled 1,1′-(3-isopropylphenylene-1,2-dioxy)bis(3-chloro-2-propanol), prepared from an equimolar amount of 3-isopropylcatechol, 0.0141 mol of amino ether and 0.0332 mol of 2-hydroxymethyl-5- and -8-isopropylbenzodioxane [n^{20}D 1.5359. Anal. ($C_{12}H_{16}O_3$) C, H] were obtained: total yield 0.0473 mol. The similarity of the total yields demonstrates that on amination of the impure bis(3-chloro-2-hydroxypropyl) ethers, the monoethers still present were converted virtually quantitatively into 2-hydroxymethyl-1,4-benzodioxanes.

1,1′-(Naphthalene-2,3-dioxy)bis(2,3-epoxypropane) (7a). A solution of 16.0 g (0.1 mol) of 2,3-dihydroxynaphthalene, 15 mL of EtOH, 37.0 g of epichlorohydrin, and 0.4 mL of 10 N NaOH was stirred under N_2 at 40 °C for 54 h. After concentration in vacuo at 40 °C, the oil was taken up in 28.0 g of epichlorohydrin and stirred vigorously with 42.0 mL of 5 N NaOH, saturated with Na_2CO_3, at room temperature for 20 h.[13] After addition of Et_2O and H_2O the product was extracted, washed, concentrated, and crystallized from Et_2O: mp 83.5–87.5 °C; yield 17.9 g (66%). The ^{1}H NMR spectrum was consistent with the structure.

Dissociation constants and partition coefficients, 1-octanol–phosphate buffer, pH 7.40, were determined as described previously.[1]

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Synthesis and Antiprotozoal Activity of 2,5-Bis(4-guanylphenyl)furans

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Eighteen substituted 2,5-bis(4-guanylphenyl)furans and related analogues, including "masked" amidines in which the guanyl function is incorporated into a heterocyclic ring, have been synthesized and their antimalarial and antitrypanosomal activity has been evaluated. None of the compounds exhibited high orders of antimalarial activity; however, 11 were very active against *Trypanosoma rhodesiense* in mice. Six compounds, including 2,5-bis(4-guanylphenyl)furan (**4**) and its 3-chloro (**32**), 3,4-dichloro (**31**), 3-methyl (**25**), 3,4-dimethyl (**20**), and 3-chloro-4-methyl (**38**) derivatives, produced cures in mice at submilligram dosage levels; the 3,4-dimethyl (**20**) analogue exhibited a prolonged curative effect providing protection for 30 days after a single dose against a challenge by *T. rhodesiense*. These six compounds are somewhat more active in this screen than stilbamidine, hydroxystilbamidine, and pentamidine. The "masked" amidines generally exhibited lower antitrypanosomal activity than their true guanyl counterparts. Compound **4** was synthesized from 1,4-di-*p*-bromophenyl-1,4-butanedione by cyclodehydrative furanization to 2,5-bis(4-bromophenyl)furan (**2**) which was allowed to react with $Cu_2(CN)_2$ to produce the corresponding bis-nitrile **3**. The latter compound was ultimately converted by way of an imidate ester into **4**. Similarly, the 3- and/or 4-substituted derivatives of **2** were employed to prepare the other members of the series.

A number of aryldiamidines have been found to be valuable for the treatment of various protozoan diseases.[1-4] Diminazene,[2] imidocarb,[3] stilbamidine,[2] hydroxystilbamidine,[2,4] pentamidine,[2,4] congocidin,[1a] and the tere-