was completely absent from the urine. The aqueous phase was brought to pH 4.6 with 0.1 M acetate buffer (2 mL) and incubated at 37 °C for 24 h with 200 μL of β-glucuronidase/arylsulfatase. The extraction with EtOAc was repeated and the extract was analyzed by HPLC.

A further 2-mL sample of urine was directly incubated with β-glucuronidase/arylsulfatase and treated and analyzed as above in order to evaluate the total amount of **3** both in the free and in the conjugated form. On the average, the amounts of **3** found in the free and in the conjugated form were respectively 140 ± 10 and 100 ± 10 μg/mL, corresponding to a ratio of about 6:4. The total amount of diol obtained after direct total enzymatic hydrolysis was 260 ± 10 μg/mL.

Determination of the Enantiomeric Excess of Diol 3. The diol (2 mg) was dissolved in pyridine (0.2 mL) and treated with (−)-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((−)-MTPA chloride, 30 mg). The mixture was stored at room temperature for 4 days, then diluted with H_2O, acidified with 10% HCl, and extracted with EtOAc. The washed (saturated $NaHCO_3$) and dried ($MgSO_4$) solution was evaporated to dryness and analyzed by HPLC (normal phase, hexane/EtOAc, 90:10, retention times of (*R,R,S*)- and (*S,S,S*)-**13**: 732 and 822 s, respectively, R_s = 2.5). When racemic **3** was used, the two diastereoisomeric bis(MTPA) esters were present in a ratio of 50:50.

Determination of the Absolute Configuration of (−)-3 via Its Bis[*p*-(dimethylamino)benzoate] 11. *p*-(Dimethylamino)benzoyl chloride (140 mg, 0.75 mmol) was added to a solution of (−)-**3** (20 mg, 0.074 mmol) in pyridine (1 mL) containing 3 mg (0.025 mmol) of *p*-(dimethylamino)pyridine, and the resulting solution was kept at 70 °C for 18 h. After cooling, the mixture was diluted with EtOAc (15 mL), washed with H_2O and aqueous 10% Na_2CO_3, dried ($MgSO_4$), and evaporated in vacuo. The crude residue was purified by preparative TLC ($CHCl_3$/MeOH, 90:10) followed by crystallization from EtOH, giving 8 mg of pure **11** (TLC): ^1H NMR ($CDCl_3$) δ 2.9 (s, 12 H, CH_3), 4.6 (s, 2 H, NH_2), 6.4 and 7.7 (AA'BB' system, 8 H, aromatic protons ortho and meta to the *N,N*-dimethylamino groups), ~6.8 (m, 2 H, C(10)H, C(11)H), 7.3 (m, 8 H, dibenzoazepine aromatic protons); IR (Nujol) 3450–3150 (NH_2), 1690 (C=O) cm^{-1}; UV λ_{max} (EtOH) 312 nm (ε 24 000); CD (EtOH) $\Delta\epsilon_{324}$ = +23, $\Delta\epsilon_{300}$ = −11.6 (see Figure 1).

Acknowledgment. This work was supported by a grant from the Ministero della Pubblica Istruzione. We thank Dr. C. Rosini for recording the CD spectra and Dr. S. Pucci for taking the FAB MS spectra.

Registry No. **1**, 298-46-4; **2**, 36507-30-9; (−)-**3**, 106758-94-5; (±)-**3**, 106680-78-8; **4**, 106680-74-4; **5**, 885-23-4; **6**, 68011-71-2; **7**, 33948-22-0; **8**, 41359-09-5; **9**, 106680-75-5; **11**, 106680-76-6; **13** (*RRS*), 106680-77-7; **13** (*SSS*), 106759-88-0; (−)-MTPA chloride, 39637-99-5; *p*-$Me_2NC_6H_4COCl$, 4755-50-4; *m*-ClC_6H_4COOOH, 937-14-4; iminostilbene, 256-96-2; epoxide hydrolase, 9048-63-9.

Synthesis and Antiarrhythmic Activity of New 3-[2-(ω-Aminoalkoxy)phenoxy]-4-phenyl-3-buten-2-ones and Related Compounds

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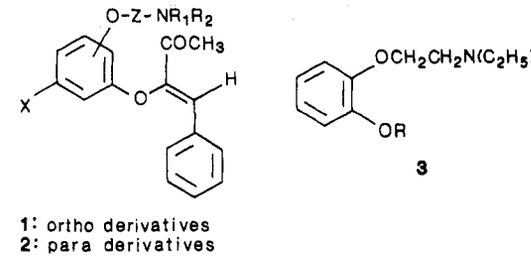
A number of the title compounds (**1**) and a few related hydroquinone derivatives (**2**) have been synthesized and tested for antiarrhythmic activity in vivo (protection against $CaCl_2$-induced ventricular fibrillation in anesthetized rat) and in vitro (ability to reduce the maximum driven frequency of an electrical stimulus in isolated rabbit atria). The effects induced by modification of the enol ether moiety in the parent compound **1a** were also examined. Many of the compounds exhibited antiarrhythmic properties stronger than quinidine and procainamide, associated with a more favorable LD_{50}/ED_{50} ratio. Compounds **1a** (LR-18,460, 3-[2-[2-(diethylamino)ethoxy]phenoxy]-4-phenyl-3-buten-2-one) and **1h** (LR-18,795, 3-[2-[3-(dimethylamino)propoxy]phenoxy]-4-phenyl-3-buten-2-one) were submitted to further antiarrhythmic testing, which confirmed their effectiveness and superiority to quinidine in all the experiments. After safety evaluation studies, both were selected for clinical investigation.

Previous pharmacological screening for new cardiovascular agents led us to discover the antiarrhythmic activity of several basic cyclic ethers of catechol, namely, aminoalkyl-substituted 1,3-benzodioxols and 1,4-benzodioxans.[1] During these studies, 3-[2-[2-(diethylamino)ethoxy]phenoxy]-4-phenyl-3-buten-2-one (**1a**), an open-chain catechol derivative, was also found to possess strong antiarrhythmic activity in an in vivo test ($CaCl_2$ intoxication in the rat). This result prompted us to prepare a series of catechol derivatives of general formula **1** and a few related hydroquinone derivatives **2** (Table I). In this paper, we report their synthesis and some preliminary pharmacological data, with particular reference to antiarrhythmic activity. Modifications of the enol ether function present in the parent compound **1a** were also performed in order to elucidate some structure–activity relationships (compounds of general formula **3**, Table II).

Chemistry. The syntheses of the new compounds **1** and **2**, listed in Table I, were performed according to the following routes (Scheme I), starting from mono enol ethers



3

1: ortho derivatives
2: para derivatives

4a, **4b**, and **5**, respectively: (A) aminoalkylation with the proper ω-chloroalkylamine or (B) alkylation with 1,3-dibromopropane or (C) 1-chloro-2,3-epoxypropane, followed by reaction with the various amines.

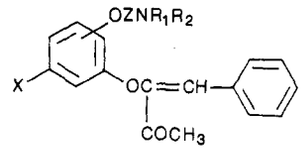
Starting catechol derivatives **4a,b** were prepared (Scheme II) by reacting the corresponding dihydroxybenzenes with (*Z*)-3-bromo-4-phenyl-3-buten-2-one according to a modification of a known procedure, which reduces the concurrent ring closure to benzodioxol and benzodioxan compounds.[2] Minor amounts of asymmetrical bis enol ethers **4c,d**, arising from a Michael-type addition of **4a,b** to the acetylenic intermediate originated by dehydrobromination of the substrate,[2] were also ob-

(1) (a) Manghisi, E.; Salimbeni, A.; Fregnan, G. B.; Vidali, M. *Eur. J. Med. Chem—Chim. Ther.* **1979**, *14*, 94 and references cited therein. (b) Salimbeni, A.; Manghisi, E.; Ferni, G.; Fregnan, G. B.; Vidali, M. *Farmaco, Ed. Sci.* **1981**, *36*, 932.

(2) Rosnati, V.; Salimbeni, A.; *Gazz. Chim. Ital.* **1977**, *107*, 271.

0022-2623/87/1830-0773$01.50/0

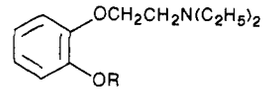
Table I. Physical and Analytical Data for 3-[2(or 4)-(ω-Aminoalkoxy)phenoxy]-4-phenyl-3-buten-2-ones



no.	basic chain position	Z	NR_1R_2	X	yield,[a] % (synth meth)	mp, °C	crystn solvent[b]	formula[c]
1a	2	$(CH_2)_2$	$N(C_2H_5)_2$	H	67 (A)	108–109	A	$C_{22}H_{27}NO_3 \cdot C_6H_8O_7$
1b	2	$(CH_2)_2$	$N[CH(CH_3)_2]_2$	H	33[d] (A)	109–111	B + C	$C_{24}H_{31}NO_3 \cdot HCl \cdot H_2O$
1c	2	$(CH_2)_2$	c-NC_4H_8	H	29 (A)	54–55	D	$C_{22}H_{25}NO_3$
1d	2	$(CH_2)_2$	c-NC_5H_{10}	H	45 (A)	121–123	A	$C_{23}H_{27}NO_3 \cdot HCl \cdot H_2O$
1e	2	$(CH_2)_2$	c-$N(CH_2CH_2)_2O$	H	50 (A)	177–179	A	$C_{22}H_{25}NO_4 \cdot HCl$[g]
1f	2	$CH_2CH(CH_3)$[e]	$N(CH_3)_2$	H	63[e] (A)	120–122	F	$C_{21}H_{25}NO_3 \cdot C_4H_4O_4$
1g	2	$(CH_2)_3$	$N(CH_3)_2$	H	29 (A)	99–101	A	$C_{21}H_{25}NO_3 \cdot C_6H_8O_7$
1h	2	$(CH_2)_3$	$N(C_2H_5)_2$	H	69 (A)	143–145	B	$C_{23}H_{29}NO_3 \cdot HCl$
1i	2	$(CH_2)_3$	$N[CH(CH_3)_2]_2$	H	51 (B)	*f*		$C_{25}H_{33}NO_3$
1l	2	$(CH_2)_3$	$NHC(CH_3)_3$	H	71 (B)	175–177	A	$C_{23}H_{29}NO_3 \cdot HCl$
1m	2	$(CH_2)_3$	c-NC_5H_{10}	H	24 (A)	111–112	A + C	$C_{24}H_{29}NO_3 \cdot C_6H_8O_7$
1n	2	$(CH_2)_3$	c-$N(CH_2CH_2)_2NCH_3$	H	76 (B)	187–189	A	$C_{24}H_{30}N_2O_3 \cdot 2C_4H_4O_4$
1o	2	$(CH_2)_2$	$N(C_2H_5)_2$	5-Cl	65[d] (A)	113–116	G	$C_{22}H_{26}ClNO_3 \cdot C_6H_8O_7$
1p	2	$(CH_2)_2$	$N[CH(CH_3)_2]_2$	5-Cl	81 (A)	73–74	E + C	$C_{24}H_{30}ClNO_3 \cdot C_4H_6O_6 \cdot 2H_2O$[h]
1q	2	$(CH_2)_2$	c-NC_5H_{10}	5-Cl	49 (A)	150–151	B	$C_{23}H_{26}ClNO_3 \cdot HCl \cdot H_2O$
1r	2	$CH_2CH(OH)CH_2$	$NHC(CH_3)_3$	H	42 (C)	155–156	A	$C_{23}H_{29}NO_4$
1s	2	$CH_2CH(OH)CH_2$	$c\text{-}N(CH_2CH_2)_2NCH_3$	H	40 (C)	161–162	A	$C_{24}H_{30}N_2O_4 \cdot 2C_4H_4O_4$
2a	4	$(CH_2)_2$	$N(C_2H_5)_2$	H	32 (A)	135–137	A	$C_{22}H_{27}NO_3 \cdot C_6H_8O_7$
2b	4	$CH_2CH(CH_3)$[e]	$N(CH_3)_2$	H	44[e] (A)	70–72	A + C	$C_{21}H_{25}NO_3 \cdot C_6H_8O_7$
2c	4	$CH_2CH(OH)CH_2$	$NHC(CH_3)_3$	H	69 (C)	73–75	A	$C_{23}H_{29}NO_4 \cdot HBr$

[a] Isolated yield (as crude base); letters refer to methods of preparation described in the Experimental Section. [b] A, EtOH; B, acetone; C, ethyl ether; D, *n*-hexane; E, 2-propanol; F, ethyl acetate; G, methyl ethyl ketone. [c] A satisfactory C, H, and N analysis was obtained for all compounds, except where noted; $C_6H_8O_7$ = citric acid; $C_4H_4O_4$ = maleic acid; $C_4H_6O_6$ = tartaric acid. [d] Isolated yield (as salt). [e] In mixture with its $CH(CH_3)CH_2$ isomer. [f] bp 212–220 °C (0.4 mm). [g] Calcd: C, 65.41. Found: C, 64.97 [h] Calcd: H, 6.70. Found: H, 6.19.

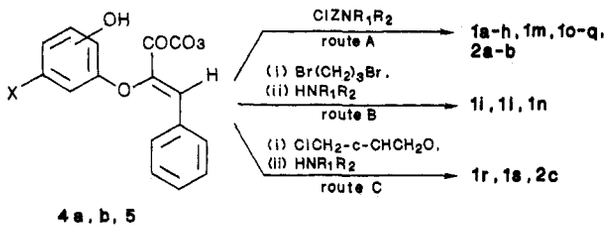
Table II. Physical and Analytical Data of Compounds 3



no.	R	yield,[a] %	mp, °C	crystn solvent[b]	formula[c]
3a	CH_2COCH_3	65	87–89	A	$C_{15}H_{23}NO_3 \cdot C_6H_8O_7$
3b	$CH_2CH(OH)CH_3$	79	108–110	B	$C_{15}H_{25}NO_3 \cdot C_6H_8O_7$
3c	$CH(CH_2C_6H_5)COCH_3$	72	83–85	A	$C_{22}H_{29}NO_3 \cdot C_6H_8O_7$
3d	$C(=CHC_6H_5)CH(OH)CH_3$	49	116–118	A	$C_{22}H_{29}NO_3 \cdot C_6H_8O_7$
3e	$CH(CH_2C_6H_5)CH(OH)CH_3$	62	94–96	A	$C_{22}H_{31}NO_3 \cdot C_6H_8O_7$
3f	$C(=CHC_6H_5)COC_6H_5$	46[d]	170–172	A + C	$C_{27}H_{29}NO_3 \cdot HCl$
3g	$C(=CHCH_3)COCH_3$	68	118–120	B	$C_{17}H_{25}NO_3 \cdot C_6H_8O_7$

[a] Isolated yield (as crude base). [b] A, EtOH; B, 2-propanol; C, ethyl ether. [c] A satisfactory C, H, and N analysis was obtained for all compounds; $C_6H_8O_7$ = citric acid. [d] Isolated yield (as hydrochloride salt).

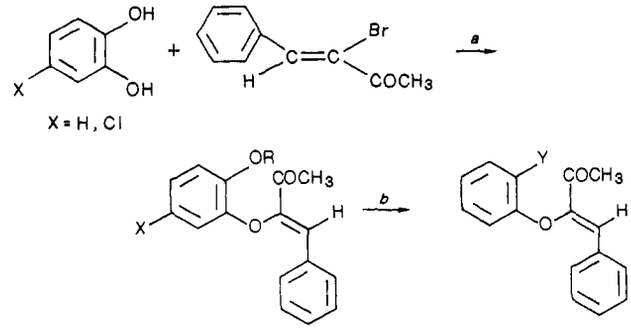
Scheme I



tained in these reactions. The position of the chlorine in compound **4b** was determined by ^{13}C NMR analysis on its methyl ether **9c**.[3]

(3) Low-power specific ^1H-decoupling experiments on compound **9c** (see ^{13}C NMR spectrum in the Experimental Section) indicate that C-1′ is coupled (J = 6.5 and 3.5 Hz) to H-3′ and H-6′, while C-2′ is coupled (J = 6.5 and 6.5 Hz) to H-4′ and H-6′. As a consequence, the chlorine atom must be located at the C-5′ position. The above ^1H–^{13}C coupling values are in good agreement with those for the corresponding three-bond (C, H) couplings (^3J = 5–11 Hz) and for the two-bond (C, H) couplings (^2J = 0–4 Hz) in substituted aromatic systems.

Scheme II



4a: X = R = H
b: X = Cl; R = H
c: X = H; R = C(C6H5)=CHCOCH3
d: X = Cl; R = C(C6H5)=CHCOCH3

6: Y = O(CH2)3Br
7: Y = OCH2-c-CHCH2O

[a] K_2CO_3–acetone. [b] $Br(CH_2)_3Br$ or $ClCH_2\text{-}c\text{-}CHCH_2O$.

The starting hydroquinone derivative **5** was obtained in low yield through the reaction of benzaldehyde with 1-

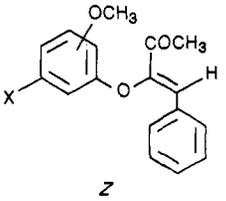
Table III. Pharmacological Data on 3-[2(or 4)-(ω-Aminoalkoxy)phenoxy]-4-phenyl-3-buten-2-ones

compd	acute toxicity[a]		antiarrhythmic activity[a]	
	mouse: LD_{50}, mg/kg ip	rat: LD_{50}, mg/kg iv	$CaCl_2$ in anesth rat: ED_{50}, mg/kg iv	elect. stim of rabbit atrium in vitro: EC_{30}, μg/mL
1a	72 (69.90–74.12)	8.9 (7.8–10.2)	0.46 (0.36–0.58)	0.7 (0.60–0.83)
1b	125 (106.0–138.3)	10.1 (9.5–10.7)	0.50 (0.41–0.63)	1.0 (0.91–2.7)
1c	45 (32.4–60.1)		1.0 (0.78–1.8)	3.0 (1.4–5.0)
1d	63 (51.7–73.8)	11.2 (9.8–12.0)	0.75 (0.62–0.83)	3.0
1e	180	30.0	5.0	6.0
1f	45 (39.0–53.8)		0.90 (0.78–1.4)	2.0 (0.99–3.7)
1g	110	13.5	0.37 (0.22–0.49)	3.0
1h	95 (81.0–110.7)	11.1 (10.4–11.8)	0.18 (0.12–0.27)	0.41 (0.07–2.1)
1i	60 (43.5–70.9)	11.4 (10.4–12.4)	0.10 (0.09–0.22)	0.32 (0.09–0.72)
1l	63 (49.3–74.6)	12.5 (10.8–13.9)	1.5 (1.1–2.4)	2.3 (0.94–4.5)
1m	62 (48.7–73.0)	6.5 (4.8–7.9)	0.20 (0.12–0.43)	1.6 (0.98–3.7)
1n	125	23.9 (22.8–25.5)	2.5 (1.0–3.9)	1.3 (0.84–2.6)
1o	170		0.60 (0.43–0.74)	2.0 (0.77–4.2)
1p	165		0.62 (0.38–0.75)	2.0 (0.73–3.1)
1q	185		0.9 (0.62–1.3)	3.0 (1.1–5.9)
1r	80 (61.1–94.5)	17.0	1.9 (0.92–3.1)	0.51 (0.23–0.83)
1s	175 (162.1–198.0)		7.5 (4.7–10.5)	10.0
2a	163 (142.0–180.3)		2.0 (0.94–3.9)	3.0 (1.2–7.3)
2b	100		3.0	3.5 (1.1–6.4)
2c	105 (92.3–116.7)		3.5	2.8 (1.0–4.4)
quinidine	175 (169.1–183.0)	48.0 (46.0–51.1)	4.7 (4.0–5.6)	3.9 (2.2–7.0)
procainamide	312 (305.9–318.2)	121.0 (110.5–132.5)	48.1 (38.6–59.6)	45.8 (24.5–85.4)

[a] Numbers in parentheses indicate 95% confidence limits calculated according to Finney.[13]

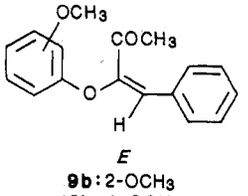
(4-hydroxyphenoxy)propan-2-one in the presence of Ac_2O and $N(C_2H_5)_3$, followed by alkaline hydrolysis of the intermediate acetate (Scheme III).

The bromo derivative **6** and the epoxides **7** and **8** were prepared from phenol precursors **4a** and **5** by reaction with 1,3-dibromopropane and epichlorohydrin, respectively. All compounds **1** and **2** were shown to have *Z* configuration; the assignment was made by comparing the chemical shifts of the vinylic protons in starting compounds **4a** and **5**, as their methyl ethers **9a** and **10a**, respectively, with those of the corresponding *E* isomers **9b** and **10b** obtained by UV irradiation of the *Z* isomers. Due to the strong deshielding effect of the near carbonyl group,[4] vinylic protons of the *Z* isomers fell in the aromatic field (about 6.8–7.7 ppm), while those of the *E* isomers appeared at 6.33 and 6.38 ppm for catechol and hydroquinone derivatives, respectively (see Experimental Section).



Z

9a: X = H; 2-OCH_3
9c: X = Cl; 2-OCH_3
10a: X = H; 4-OCH_3

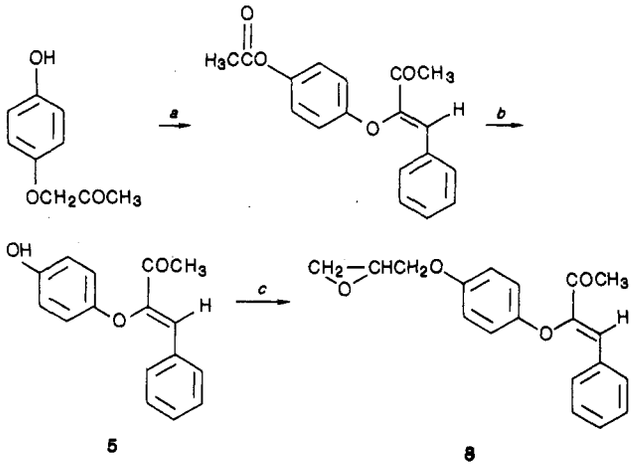


E

9b: 2-OCH_3
10b: 4-OCH_3

Compounds **3** (Table II), characterized by a modified enol ether function, were synthesized as follows. Compounds **3a** and **3f** were prepared by aminoalkylation of the corresponding catechol monoethers, while **3c** was obtained by catalytic hydrogenation of the double bond in **1a**. Carbinols **3b,d,e** were obtained by $LiAlH_4$ reduction of the ketone in the corresponding compounds. Interestingly, compound **3g** was prepared by ring opening of 2-acetyl-2,3-dihydro-3-methyl-1,4-benzodioxin, following a general procedure, which will be discussed in detail in a forthcoming paper.[5] The intermediate 2-(2-hydroxyphen-

Scheme III



[a] benzaldehyde, $(CH_3CO)_2O$, $N(C_2H_5)_3$. [b] NaOH. [c] $ClCH_2$-c-$CHCH_2O$.

oxy)-1,3-diphenylpropan-1-one (**11**), required for **3f**, was prepared by reacting catechol with 2,3-dibromo-1,3-diphenylpropan-1-one, according to the procedure described for **4a**.

Results and Discussion

All new compounds were tested in mice by the ip route for acute toxicity, in rats by the iv route for protection against $CaCl_2$-induced ventricular fibrillation, and in isolated rabbit atria to evaluate the ability to reduce the maximum driven frequency of an electrical stimulus. Many of the compounds were also submitted to an iv acute toxicity test in rats. Quinidine and procainamide were used as standards. The pharmacological data, which are summarized in Tables III and IV, allow the following considerations in terms of structure–activity relationships concerning mainly (a) the nature of amine substituent on the side chain, (b) the nature and position of the side chain, and (c) the modification of the enol ether function.

(4) Rosnati, V.; Saba, A.; Salimbeni, A.; Vettori, U. *Gazz. Chim. Ital.* **1981**, *111*, 249.

(5) Rosnati, V.; Salimbeni, A., submitted for publication in *Tetrahedron*.

Table IV. Pharmacological Data on Compounds 3

no.	acute toxicity[a] mouse: LD_{50}, mg/kg ip	acute toxicity[a] rat: LD_{50}, mg/kg iv	antiarrhythmic activity[a] $CaCl_2$ in anesth rat: ED_{50}, mg/kg iv	antiarrhythmic activity[a] elect. stim of rabbit atrium in vitro: EC_{30}, μg/mL
3a	125 (102.3–142.5)		7.0 (5.8–9.2)	15.0
3b	187 (167.4–201.8)		7.1 (5.3–9.6)	15.0
3c	92 (88.1–95.1)	11.7 (10.2–13.4)	0.75 (0.52–0.94)	10.0
3d	110		1.5 (0.91–3.4)	1.9 (0.88–3.1)
3e	85 (69.1–99.3)		1.0 (0.84–2.9)	2.5 (1.4–5.7)
3f	125 (112.1–144.2)		1.4 (0.83–3.1)	2.8 (1.3–6.2)
3g	80		3.0 (1.2–4.8)	5.0 (2.7–7.8)

[a] Numbers in parentheses indicate 95% confidence limits calculated according to Finney.[13]

Table V. Further Experimental Data on the Antiarrhythmic Activity of Compounds 1a and 1h

test	route[a]	ED_{50}, mg/kg[b,c] 1a	1h	quinidine
$CaCl_2$ in anesth rat	ipv	2.3 (1.3–4.9)	0.6 (0.51–0.83)	13.5 (9.7–17.4)
$CaCl_2$ in conscious rat	iv	0.88 (0.45–1.7)	0.3 (0.15–0.48)	3.2 (2.8–4.5)
$CaCl_2$ in conscious rat	po	13.6 (8.2–22.8)	35.0 (28.0–49.9)	47.7 (34.0–67.1)
epinephrine in postinfarcted conscious dog	iv	2.0*	1.0*	1.0**
infarcted conscious dog	iv	2.0*	1.0*	5.5***
aconitine in anesth mouse: init arrhythmia	iv	7.5 (4.6–9.2)	4.3 (3.8–5.6)	15.2 (12.7–17.2)
aconitine in anesth mouse: ventric tachycardia	iv	11.0 (9.4–13.5)	4.9 (3.7–6.2)	14.0 (11.9–18.0)
aconitine in anesth mouse: init arrhythmia	po	132.0 (98.0–155.4)	82.0 (59.0–93.2)	122.0 (115.0–143.7)
aconitine in anesth mouse: ventric tachycardia	po	149.0 (128.1–160.4)	83.0 (61.4–97.2)	158.0 (138.2–170.1)

[a] ipv; = portal vein; iv = ear or caudal vein. [b] (*) Activity lasting for 15 min; (**) activity lasting for 30 min; (***) activity lasting for 1 h. [c] Numbers in parentheses indicate 95% confidence limits calculated according to Finney.[13]

Table VI. Activity on Heart Rate and on Blood Electrolytes and Local Anesthetic Properties of Compounds 1a and 1h

compd	heart rate (anesth rat) iv[a] dose, mg/kg	iv[a] act., %	ipv[b] dose, mg/kg	ipv[b] act., %	blood electrolytes (rat serum) K^+ dose, mg/kg iv	K^+ act., %	Na^+ dose, mg/kg iv	Na^+ act., %	Ca^{2+} dose, mg/kg iv	Ca^{2+} act., %	local anesthesia (tail-clip in mouse): EC_{50}, μg/mL id[c]
1a	1	−15	2	−1	5	+12	5	0[d]	5	0	0.01 (0.0060–0.175)
1h	1	−6	1	+4	5	−8	5	0	5	0	0.0099 (0.006–0.149)
quinidine	5	−30	14	−36	20	+3	20	0	20	0	0.0098 (0.0089–0.016)

[a] iv = femoral vein. [b] ipv = portal vein. [c] id = intradermal injection; EC_{50} = effective concentration that caused local anesthesia in 50% of the mice. Numbers in parentheses indicate 95% confidence limits calculated according to Finney.[13] [d] 0 = inactive.

Amine Group. Variation of the amine group showed that in the $CaCl_2$ test good antiarrhythmic activity is mainly associated with tertiary amines (compounds **1a,-b,g–i**). Cyclic amines showed low or no activity, with the exception of piperidines **1d** and **1m**, which however were more toxic. Compounds **1a,h,i** were also very active in isolated rabbit atria.

Side Chain Carrying the Amine Group. Examination of the pairs of homologous compounds (for example, **1a** and **1h**, **1b** and **1i**, **1d** and **1m**) suggests that a three-carbon chain is favorable for both in vivo and in vitro activities. Hydroxylation of the chain resulted in strong activity only in vitro (compare **1l** with **1r**), while branching of the chain seemed to be unfavorable (compare **1f** and **1g**). Hydroquinone derivatives, although less toxic, possessed inferior antiarrhythmic properties (compare **1a** with **2a**, **1f** with **2b**, **1r** with **2c**).

Enol Ether Function. All modifications of the enol ether function present in the parent compound **1a** proved to lower activity, particularly the elimination of the phenyl group (compounds **3a,b,g**). This decrease in activity might be related to the much lower lipophilicity of the modified compounds.[6]

Compounds **1o–q**, which have a chlorine atom in the aromatic ring, appeared to be less toxic and slightly less active than the corresponding unsubstituted compounds **1a,b,d**.

The data reported in Tables III and IV indicated that **1a**, **1h**, and **1i** were the most promising compounds, showing stronger antiarrhythmic properties than quinidine and procainamide, associated with a more favorable LD_{50}/ED_{50} ratio in rats by the iv route. The corresponding ratios for compounds **1a,h,i** were 19.3, 61.7, and 11.4 vs. 10.2 and 2.5 for quinidine and procainamide, respectively.

Compounds **1a** and **1h**, which had no sympathetic or parasympathetic activity in vitro and in vivo, were submitted to further studies to determine the extent and the relative potency of their antiarrhythmic effectiveness in comparison with quinidine. As can be seen from the data presented in Table V, both compounds confirmed their effectiveness, being more active than quinidine in all the experiments. Compound **1h** was by far the most effective, except when administered in conscious rats intoxicated with $CaCl_2$. The low activity in this test cannot be ascribed to a first-pass effect, since the product maintained a higher activity than **1a** and quinidine when injected into the portal vein. Studies in vitro indicate that the compounds are rapidly inactivated (within 10 min) when incubated with rat plasma at 37 °C. The data reported in Table VI

(6) The R_m chromatographic parameter was used as an expression of the lipophilic character of the molecules. The found values, determined by means of a reversed-phase TLC technique,[7] were the following: 0.385, 0.359, 0.890, and 1.671 for **3a**, **3b**, **3g**, and **1a**, respectively.

(7) Biagi, G. L.; Barbaro, A. M.; Gamba, M. F.; Guerra, M. C. *J. Chromatogr.* **1969**, *41*, 371.

show that both **1a** and **1h** had a local anesthetic activity comparable to that of quinidine by the tail clip method in the mouse. Na^+, K^+, and Ca^{2+} concentrations in rat serum and the heart rate of the rat were not altered, while quinidine caused bradycardia.

These pharmacological results suggest that the antiarrhythmic activity of these compounds cannot be due to blockage of β-adrenergic receptors and slow Ca^{2+} influx through membranes of cardiac cells. The local anesthetic activity is also too weak to be considered a primary event. Studies are in progress to determine their mechanism of action.

After safety evaluation studies, both compounds were selected for human investigation. Preliminary clinical results indicate that compound **1a** (LR-18,460) effectively reduces the number of ectopic beats when injected intravenously into patients affected by ventricular arrhythmias, but the antiarrhythmic effect seems to be short-lasting.

Experimental Section

Melting points are uncorrected and were taken on a Büchi apparatus. IR spectra were recorded on a Perkin-Elmer 237 spectrophotometer. ^1H NMR spectra at 60 MHz were determined with a Perkin-Elmer R-24 spectrometer, while ^1H NMR spectra at 300 MHz and ^{13}C NMR spectra were determined with a Bruker LXP 300 instrument, with Me_4Si as internal standard. Microanalyses were performed by Istituto di Chimica Organica, University of Milan; analytical results are within ±0.4% of theoretical values. Mass spectra were obtained on a Hitachi Perkin-Elmer RMV-6D single-focusing spectrometer.

(*Z*)-3-(2-Hydroxyphenoxy)-4-phenyl-3-buten-2-one (4a). A solution of catechol (75 g, 0.68 mol) and (*Z*)-3-bromo-4-phenyl-3-buten-2-one[8] (146 g, 0.65 mol) in anhydrous acetone (270 mL) was refluxed (4 h) with stirring in the presence of K_2CO_3 (190 g, 1.38 mol). After cooling, the mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in ethyl ether and the solution repeatedly washed with 10% NaOH, whereby an orange solid separated. The latter was filtered, washed with ethyl ether, and dried over P_2O_5 to give 126 g (70%) of **4a** as sodium salt: mp 122–124 °C; IR (Nujol) ν_{max} 3350 (br), 1670, 1630 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.22 (3 H, s, $COCH_3$), 5.74–8.05 (10 H, m Arom, =CH). According to the literature,[2] the title compound (**4a**) as free phenol was obtained from a solution of the salt in H_2O, acidification with dilute HCl, and extraction with CH_2Cl_2: mp 78–79 °C (from cyclohexane).

3-[2-(3-Oxo-1-phenyl-1-butenyloxy)phenoxy]-4-phenyl-3-buten-2-one (4c). After filtration of the sodium salt of **4a** (see above), the ethereal mother liquors were separated from the alkaline layer, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The residue was triturated with isopropyl ether to give white crystals (2.3 g) of the title compound (**4c**) as one isomer of undetermined configuration: mp 132–135 °C; IR (Nujol) ν_{max} 1670, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (3 H, s, $COCH_3$), 2.53 (3 H, s, $COCH_3$), 6.19 (1 H, s, =C*H*$COCH_3$), 6.67–6.80 (4 H, m, Arom), 7.18–7.35 (7 H, m, Arom, =C*H*C_6H_5), 7.55–7.72 (4 H, m, Arom); MS, *m/e* 398 (M^+), 383 (M − 15), 355 (M − $COCH_3$). Anal. ($C_{26}H_{22}O_4$) C, H.

(*Z*)-3-(5-Chloro-2-hydroxyphenoxy)-4-phenyl-3-buten-2-one (4b). The reaction was carried out according to the method described for **4a**, starting from 4-chlorocatechol (100 g, 0.69 mol) and (*Z*)-3-bromo-4-phenyl-3-buten-2-one[8] (155 g, 0.62 mol). Workup of the crude reaction mixture as previously reported gave the title compound (**4b**) as its dihydrate sodium salt (23 g, 11%): mp 128–130 °C; IR (Nujol) ν_{max} 3440 (br), 1670, 1630 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.34 (3 H, s, $COCH_3$), 6.65–8.20 (9 H, m, Arom). Acidification with 1:1 HCl of the alkaline washings and extraction with ethyl ether gave an additional amount of **4b** (16 g, 16%) as free phenol, which was purified by crystallization from isopropyl ether: mp 131–133 °C; IR (Nujol) ν_{max} 3460, 1670, 1630 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.82 (3 H, s, CH_3), 2.38 (3 H, s, $COCH_3$), 6.12 (1 H, s, =CH hemiketalic form), 6.66–7.97 (17 H, m, Arom, =CH). Anal. ($C_{16}H_{13}ClO_3$) C, H.

3-[5-Chloro-2-(3-oxo-1-phenyl-1-butenyloxy)phenoxy]-4-phenyl-3-buten-2-one (4d). After filtration of the sodium salt of **4b** (see above), the ethereal mother liquors were separated from the alkaline layer, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The residue was crystallized from benzene to give light-yellow crystalls (4.2 g) of the title compound (**4d**) as a mixture of isomers: mp 159–161 °C; IR (Nujol) ν_{max} 1670, 1630 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 2.41, 2.45, 2.53 and 2.54 (3 H, s, $COCH_3$), 6.25 and 6.30 (1 H, s, =C*H*$COCH_3$), 6.67–6.91 (3 H, m, Arom), 7.35–7.53 (7 H, m, Arom, =C*H*C_6H_5), 7.68–7.87 (4 H, m, Arom); MS, *m/e* 432 (M^+), 417 (M − 15), 389 (M − $COCH_3$). Anal. ($C_{26}H_{21}ClO_4$) C, H. From column chromatography of a sample of the mother liquors (silica gel 40; benzene–hexane, 4:1, as eluent), the following products were also isolated. *trans*-2-Acetyl-6(or 7)-chloro-2,3-dihydro-3-phenyl-1,4-benzodioxin, as a light-yellow solid: mp, 108–110 °C; IR (Nujol) ν_{max} 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (3 H, s, $COCH_3$), 4.66 (1 H, d, CH ring, *J* = 6 Hz), 5.24 (1 H, d, CH ring, *J* = 6 Hz), 6.85–7.06 (3 H, m, Arom), 7.36 (5 H, s, Arom). Anal. ($C_{16}H_{13}ClO_3$) C, H. (5-Chloro-2-phenyl-1,3-benzodioxol-2-yl)propan-2-one, as a yellow oil: IR (neat) ν_{max} 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (3 H, s, $COCH_3$), 3.33 (2 H, s, CH_2), 6.70–6.90 (3 H, m, Arom), 7.15–7.65 (5 H, m, Arom). Anal. ($C_{16}H_{13}ClO_3$) C, H.

(*Z*)-3-(4-Hydroxyphenoxy)-4-phenyl-3-buten-2-one (5). A mixture of 3-(4-hydroxyphenoxy)propan-2-one (150 g, 0.91 mol),[9] benzaldehyde (96 g, 0.91 mol), acetic anhydride (240 mL), and triethylamine (120 mL) was heated at reflux for 48 h. After cooling, the reaction mixture was poured onto ice and repeatedly extracted with ethyl ether. The organic layers were collected, washed with H_2O, and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was fractionated under vacuum. The main fraction (bp 160–200 °C (1 mmHg)) (which solidified on standing) was crystallized from EtOH to give 90 g (27% yield) of 3-(4-acetoxyphenoxy)-4-phenyl-3-buten-2-one: mp 103–104 °C; IR (Nujol) ν_{max} 1750, 1680, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21 (s, 3 H, $COCH_3$), 2.24 (s, 3 H, $COCH_3$), 6.85–7.88 (m, 10 H, Arom, =CH). It was heated at reflux for 30 min with an ethanolic solution of NaOH (14 g in 1.2 L). After elimination of the solvent, the residue was partitioned between H_2O and ethyl ether. The ethereal phase was separated, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The residue was crystallized from benzene to give **5** (63 g, 82%) as a light-yellow solid: mp 133–134 °C; IR (Nujol) ν_{max} 3300, 1670, 1630 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.25 (3 H, s, $COCH_3$), 6.90–8.00 (11 H, m, Arom, =CH), 8.10 (1 H, s, OH, disappears after D_2O). Anal. ($C_{16}H_{14}O_3$) C, H.

(*Z*)-3-[2-(3-Bromopropoxy)phenoxy]-4-phenyl-3-buten-2-one (6). To a solution of 1,3-dibromopropane (219 g, 1.1 mol) in 1 L of MEK was added compound **4a** as sodium salt (100 g, 0.36 mol) portionwise with stirring at 60 °C. After 18 h at reflux, the reaction mixture was cooled and the solid was filtered off. The mother liquors were evaporated to dryness, and the residue was dissolved in ethyl ether. After repeated washings with 10% NaOH and H_2O to neutrality, the ethereal solution was dried (Na_2SO_4) and evaporated to dryness. The residue was crystallized from isopropyl ether to give **6** (51 g, 37%) as white crystals: mp 82–83 °C; IR (Nujol) ν_{max} 1680, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (3 H, s, $COCH_3$), 2.35 (2 H, q, $CH_2CH_2CH_2$), 3.65 (2 H, t, CH_2Br), 4.35 (2 H, t, OCH_2), 6.75–7.85 (10 H, m, Arom, =CH). Anal. ($C_{19}H_{19}BrO_3$) C, H.

(*Z*)-3-[2-(2,3-Epoxypropoxy)phenoxy]-4-phenyl-3-buten-2-one (7). To a mixture of **4a** as sodium salt (20 g, 0.07 mol) and NaOH (3.2 g) in H_2O (800 mL) was added 1-chloro-2,3-epoxypropane (7.1 g, 0.076 mol). After 48 h of stirring at room temperature, the precipitate was collected by filtration and crystallized from isopropyl ether to give **7** (6.9 g, 31%) as light yellow crystals: ^1H NMR ($CDCl_3$) δ 2.29 (3 H, s, $COCH_3$), 2.81 (2 H, m, c-$CHCH_2O$), 3.40 (1 H, m, c-$CHCH_2O$), 4.10–4.43 (2 H, m, OCH_2), 6.75–7.98 (10 H, m, Arom, =CH). Anal. ($C_{19}H_{18}O_4$) C, H.

(*Z*)-3-[4-(2,3-Epoxypropoxy)phenoxy]-4-phenyl-3-buten-2-one (8). A mixture of **5** (20 g, 0.079 mol), K_2CO_3 (54 g), and

(8) Cromwell, N. H.; Cram, D. J.; Harris, C. E. *Organic Syntheses*; Wiley: New York, 1965; Collect. Vol. III, p 125.

(9) Kipper, H.; Randsepp, H. *Tr. Tallin. Politekh. Inst., Ser. A* **1965**, *230*, 67; *Chem. Abstr.* **1967**, *66*, 10800*b*.

1-chloro-2,3-epoxypropane (36 g) in MEK (0.6 L) was refluxed with stirring for 18 h. After cooling, the solid was filtered off and the solution was evaporated to dryness. The oily residue was dissolved in ethyl ether, and the solution was repeatedly washed with 10% NaOH and H_2O. After drying (Na_2SO_4), the solvent was evaporated to dryness to give **8** as an oil (17.4 g, 71.3%), which was used for the next step without further purification.

(*Z*)-3-(2-Methoxyphenoxy)-4-phenyl-3-buten-2-one (9a). The compound was obtained from **4a** as sodium salt by reaction with CH_3I according to the literature:[2] bp 190–195 °C (0.4 mmHg); ^1H NMR ($CDCl_3$) δ 2.25 (3 H, s, $COCH_3$), 3.97 (3 H, s, OCH_3), 6.80–7.70 (10 H, m, Arom, =CH).

(*E*)-3-(2-Methoxyphenoxy)-4-phenyl-3-buten-2-one (9b). A solution of the *Z*-isomer **9a** (1 g) in anhydrous acetone (900 mL) was irradiated with a UV lamp for 6 h. After elimination of the solvent, the oily residue was chromatographed on silica gel 40 (eluent: benzene) to give pure *E* isomer (0.6 g, 60%) as an oil: bp 175–180 °C (0.3 mmHg); ^1H NMR ($CDCl_3$) δ 2.30 (3 H, s, $COCH_3$); 3.90 (3 H, s, OCH_3), 6.33 (1 H, s, =CH), 6.90–7.55 (9 H, s, Arom); MS, *m/e* 268 (M^+).

(*Z*)-3-(5-Chloro-2-methoxyphenoxy)-4-phenyl-3-buten-2-one (9c). The compound was easily prepared (80% yield) by reaction of **4b** with CH_3I in acetone in the presence of K_2CO_3: mp 117–119 °C (from EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (3 H, s, $COCH_3$), 3.86 (3 H, s, OCH_3), 6.71–8.03 (9 H, m, Arom, =CH); ^{13}C NMR (25.2 MHz, $CDCl_3$) δ 25.71 (1-CH_3), 56.39 (2'-OCH_3), 113.59 (C-3'), 114.83, and 122.69 (C-6' and C-4'), 125.65 (C-5'), 126.31 (C-4), 128.69 and 130.56 (C-2'', C-6'', C-3'', and C-5''), 129.91 (C-4''), 132.05 (C-1''), 145.82 (C-1'), 147.03 (C-3), 147.94 (C-2').

(*Z*)-3-(4-Methoxyphenoxy)-4-phenyl-3-buten-2-one (10a). A mixture of **5** (5.1 g, 0.02 mol), K_2CO_3 (31 g, 0.022 mol), and CH_3I (2.5 g, 0.06 mol) in acetone (100 mL) was refluxed for 24 h with stirring. Filtration of the solid and evaporation to dryness gave the compound as an oil, which was purified by distillation in vacuo (3.5 g, 65%): bp 200–215 °C (0.4 mmHg); ^1H NMR ($CDCl_3$) δ 2.23 (3 H, s, $COCH_3$), 3.75 (3 H, s, OCH_3), 6.80–7.70 (10 H, m, Arom, =CH); MS, *m/e* 268 (M^+).

(*E*)-3-(4-Methoxyphenoxy)-4-phenyl-3-buten-2-one (10b). The compound was prepared by isomerization of the *Z*-isomer **10a** (1 g) by a UV lamp according to the method described for the corresponding 2-methoxy derivative. Column chromatography on silica gel 40 (eluent: hexane–benzene, 9:1) gave the compound (0.35 g, 35%) as an oil: ^1H NMR ($CDCl_3$) δ 2.22 (3 H, s, $COCH_3$), 3.77 (3 H, s, OCH_3), 6.38 (1 H, s, =CH), 6.70–7.82 (9 H, m, Arom); MS, *m/e* 268 (M^+).

2-(2-Hydroxyphenoxy)-1,3-diphenyl-2-propen-1-one (11). The title compound was prepared according to the method described for **4a**, starting from 2,3-dibromo-1,3-diphenylpropan-1-one (30 g, 0.081 mol) and catechol (9.3 g, 0.085 mol). From the alkaline washings, after acidification with 1:1 HCl, extraction with ethyl ether, and evaporation to dryness, crude **11** was obtained as an oil. Treatment with H_2O–EtOH, 4:1, gave a solid, which was crystallized from isopropyl ether to give pure **6** (5 g, 19%): mp 118–120 °C; IR (Nujol) ν_{max} 3510, 1655, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.75–8.15 (11 H, m, Arom, =CH, OH). Anal. ($C_{21}H_{16}O_3$) C, H.

General Methods for the Preparation of 3-[2(or 4)-(ω-Aminoalkoxy)phenoxy]-4-phenyl-3-buten-2-ones (Table I). Method A. Example a. (*Z*)-3-[2-[2-(Diethylamino)ethoxy]phenoxy]-4-phenyl-3-buten-2-one (1a). To a suspension of **4a** (27 g, 0.1 mol) as sodium salt in acetone (500 mL) was added 2-(diethylamino)ethyl chloride (14.9 g, 0.11 mol) dropwise with stirring. After the reaction mixture was heated at reflux for 35 h, it was cooled, filtered, and evaporated to dryness. The residue was dissolved in dilute HCl and the solution extracted with CH_2Cl_2. The aqueous phase was made alkaline with 10% NaOH and repeatedly extracted with CH_2Cl_2. The organic layers were collected, washed with 10% NaOH and H_2O, and dried (Na_2SO_4). The solvent was removed and the oily residue distilled in vacuo to give 23.7 g of **1a** (67%): bp 202–205 °C (0.8 mmHg); IR (neat) ν 1690, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (t, 6 H, CH_3), 2.25 (s, 3 H, $COCH_3$), 2.42–3.05 (m, 6 H, $CH_2N(CH_2)_2$), 4.18 (t, 2 H, OCH_2), 6.62–7.80 (m, 10 H, Arom, =CH).

To a solution of this material in 2-propanol (50 mL) was added a solution of citric acid (14.3 g, 1 equiv) in 2-propanol (30 mL). The citrate salt that precipitated was triturated with ethyl ether, filtered, and crystallized from EtOH: mp 108–109 °C. Anal. ($C_{28}H_{35}NO_{10}$) C, H, N.

Example b. (*Z*)-3-[4-[2-(Diethylamino)ethoxy]phenoxy]-4-phenyl-3-buten-2-one (2a). To a solution of **5** (15 g, 0.059 mol) in acetone (600 mL) were added K_2CO_3 (8.6 g) and 2-(diethylamino)ethyl chloride (9.6 g, 0.04 mol). The mixture was refluxed for 15 h, then cooled, filtered, and evaporated to dryness. After the workup as reported for **1a**, the oily residue was purified by distillation in vacuo to give **2a** (6.7 g, 32%): bp 248–250 °C (1 mmHg); IR (neat) ν_{max} 1700, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (t, 6 H, CH_3), 2.20 (s, 3 H, $COCH_3$), 2.40–2.95 (m, 6 H, $CH_2N(CH_2)_2$), 3.97 (t, 2 H, OCH_2), 6.68–7.85 (m, 10 H, Arom, =CH). This material was converted to the citrate salt as described above: mp 135–137 °C (from EtOH). Anal. ($C_{28}H_{35}NO_{10}$) C, H, N.

Method B. (*Z*)-3-[2-[3-(*tert*-Butylamino)propoxy]phenoxy]-4-phenyl-3-buten-2-one (11). A mixture of **6** (18 g, 0.048 mol), *tert*-butylamine (10.5 g, 0.14 mol), and KI as catalyst in xylene (150 mL) was heated at reflux for 45 h. After cooling, the precipitate was filtered and the solution was evaporated to dryness. The residue was crystallized from *n*-hexane to give **11** (12.6 g, 71%) as free base: mp 61–63 °C; IR (Nujol) ν_{max} 1685, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (9 H, s, $C(CH_3)_3$), 2.02 (2 H, q, $CH_2CH_2CH_2$), 2.22 (3 H, s, $COCH_3$), 2.77 (2 H, t, CH_2NH), 4.14 (2 H, t, OCH_2), 6.62–7.77 (10 H, m, Arom, =CH). A solution of this material in anhydrous ethyl ether was treated with an ethanolic solution of HCl. The precipitate was collected by filtration and crystallized from EtOH to give **11** as hydrochloride: mp 175–177 °C. Anal. ($C_{23}H_{30}ClNO_3$) C, H, N.

Method C. (*Z*)-3-[2-[2-Hydroxy-3-(4-methylpiperazino)-propoxy]phenoxy]-4-phenyl-3-buten-2-one (1s). A mixture of epoxide **7** (20 g, 0.064 mol), 4-methylpiperazine (7 g, 0.07 mol), and EtOH (100 mL) was refluxed for 36 h. The solvent was evaporated, and the residue was triturated with ethyl ether. Filtration and evaporation to dryness of the mother liquors gave **1s** as an oil (10.5 g, 40%), which solidified by treatment with *n*-hexane: IR (neat) ν_{max} 1790, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (6 H, s, $COCH_3$, NCH_3), 2.54 (10 H, m, CH_2-c-$N(CH_2)_2NH(CH_2)_2$), 4.13 (3 H, m, OCH_2, $CHOH$), 4.56 (1 H, s, CH), 6.12–7.84 (10 H, m, Arom, =CH). This material was converted to the maleate salt as described above for the citrate salt: mp 161–162 °C (from EtOH). Anal. ($C_{32}H_{38}N_2O_{10}$) C, H, N.

1-[2-[2-(Diethylamino)ethoxy]phenoxy]propan-2-one (3a). The reaction was performed according to method A by heating at reflux for 28 h a mixture of 1-(2-hydroxyphenoxy)propan-2-one[10] as sodium salt (5 g, 0.266 mol) and 2-(diethylamino)ethyl chloride (4 g, 0.029 mol) in acetone (100 mL). The crude reaction mixture was purified by distillation to give **3a** as an oil (4.6 g, 65%): bp 190–195 °C (0.4 mmHg); IR (neat) ν_{max} 1725 cm^{-1}; ^1H NMR δ 1.00 (6 H, t, CH_3), 2.20 (3 H, s, $COCH_3$), 2.55 (4 H, q, CH_2CH_3), 2.80 (2 H, t, CH_2N), 3.97 (2 H, t, OCH_2), 4.35 (2 H, s, CH_2CO), 6.80 (4 H, m, Arom). This material was converted to the citrate salt as described above: mp 91–92 °C (from absolute EtOH). Anal. ($C_{21}H_{31}NO_{10}$) C, H, N.

1-[2-[2-(Diethylamino)ethoxy]phenoxy]propan-2-ol (3b). To a suspension of $LiAlH_4$ (0.79 g) in anhydrous ethyl ether (150 mL) was added a solution of **3a** as free base (10 g, 0.038 mol) in anhydrous ethyl ether (50 mL) dropwise with stirring. After an additional 3 h at reflux, the mixture was cooled and H_2O was carefully added. Filtration and evaporation of the solvent gave **3b** as an oil, which was purified by distillation (8 g, 79%): bp 175–180 °C (0.3 mmHg); IR (neat) ν_{max} 3350 cm^{-1}; ^1H NMR (CCl_4) δ 0.78–1.95 (8 H, m, $CHCH_3$, CH_2CH_3), 2.35–2.95 (6 H, m, $CH_2N(CH_2)_2$), 3.65–4.17 (5 H, m, OCH_2CHOH), 4.57 (1 H, s, OH, disappears after D_2O), 6.87 (4 H, s, Arom). This material was converted to the citrate salt as described above: mp 108–110 °C (from absolute EtOH). Anal. ($C_{21}H_{33}NO_{10}$) C, H, N.

3-[2-[2-(Diethylamino)ethoxy]phenoxy]-4-phenylbutan-2-one (3c). A solution of **1a** as free base (20 g, 0.057 mol) in EtOH (500 mL) was hydrogenated at room temperature and atmospheric pressure in the presence of 5% Pd/C (2 g). After the theoretical

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H_2 absorption, the solution was filtered through a Celite pad and evaporated to dryness. The oily residue was distilled in vacuo to give **3c** as a yellow oil (14.4 g, 72%): bp 180–185 °C (0.4 mmHg); IR (neat) ν_{max} 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (6 H, t, CH_3), 2.10 (3 H, s, $COCH_3$), 2.40–2.95 (6 H, m, $CH_2N(CH_2)_2$), 3.10 (2 H, d, $CH_2C_6H_5$), 4.02 (2 H, t, OCH_2), 4.63 (1 H, t, OCH), 6.45–7.40 (9 H, m, Arom). This material was converted to the citrate salt as described above: mp 83–85 °C (from absolute EtOH). Anal. ($C_{28}H_{37}NO_{10}$) C, H, N.

3-[2-[2-(Diethylamino)ethoxy]phenoxy]-4-phenyl-3-buten-2-ol (3d). The title compound was prepared according to the procedure described for **3b**, starting from **1a** as free base (10 g, 0.028 mol). Treatment of the oily reaction product with *n*-hexane gave **3d** as a solid (5 g, 49%): IR (Nujol) ν_{max} 3150 (br), 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (6 H, t, CH_2CH_3), 1.35 (3 H, d, CH_3), 2.35–2.90 (6 H, m, $CH_2N(CH_2)_2$), 3.97 (2 H, t, OCH_2), 4.23 (1 H, q, CHOH), 6.02 (1 H, s, =CH), 6.76–7.86 (9 H, m, Arom). This material was converted to the citrate salt as described above: mp 116–118 °C (from absolute EtOH). Anal. ($C_{28}H_{37}NO_{10}$) C, H, N.

3-[2-[2-(Diethylamino)ethoxy]phenoxy]-4-phenylbutan-2-ol (3e). The title compound was prepared according to the procedure described for **3b**, starting from **3c** as free base (8 g, 0.022 mol). The crude reaction product was distilled to give **3e** as a light-yellow oil (5 g, 62%): bp 230–235 °C (0.4 mmHg); IR (neat) ν_{max} 3400 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (6 H, t, CH_2CH_3), 1.23 (3 H, d, $CHCH_3$), 2.40–3.11 (8 H, m, $CH_2C_6H_5$, $CH_2N(CH_2)_2$), 3.58–4.30 (5 H, CHOH, OCH_2, OCH), 6.75–7.40 (9 H, m, Arom). This material was converted to the citrate salt as described above: mp 94–95 °C (from absolute EtOH). Anal. ($C_{28}H_{29}NO_{10}$) C, H, N.

2-[2-[2-(Diethylamino)ethoxy]phenoxy]-1,3-diphenyl-2-propen-1-one (3f). The reaction was performed according to method A, by refluxing for 34 h a mixture of **11** (10.5 g, 0.033 mol), K_2CO_3 (4.8 g, 0.034 mmol), and 2-(diethylamino)ethyl chloride (5.65 g, 0.04 mol) in acetone (250 mL). The crude reaction product was converted to the hydrochloride salt as described for **11**. Crystallization from EtOH–Et_2O gave 7 g of **3f** as hydrochloride (46%): mp 170–172 °C; IR (Nujol) ν_{max} 2400, 1675, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (6 H, t, CH_3), 2.75–3.05 (7 H, m, $CH_2N(CH_2)_2$, HCl), 6.65–7.95 (15 H, m, Arom, =CH). Anal. ($C_{27}H_{30}ClNO_3$) C, H, N.

(*Z*)-3-[2-[2-(Diethylamino)ethoxy]phenoxy]-3-penten-2-one (3g). A mixture of 2-acetyl-2,3-dihydro-3-methyl-1,4-benzodioxin[11] (7.5 g, 0.039 mol), K_2CO_3 (10.8 g), and 2-(diethylamino)ethyl chloride (5.83 g, 0.043 mol) in anhydrous acetone (75 mL) was refluxed with stirring for 12 h. The solid was filtered off, and the mother liquors were evaporated to dryness. The residue was partitioned between ethyl ether and H_2O. The ethereal phase was separated and evaporated to dryness to give **3g** as an oil (7.1 g, 68%): IR (Nujol) ν_{max} 1700, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (6 H, t, CH_3), 1.74 (3 H, d, $=CHCH_3$), 2.20 (4 H, s, $COCH_3$), 2.64 (4 H, q, NCH_2CH_3), 2.90 (2 H, t, OCH_2CH_2), 4.16 (2 H, t, OCH_2), 6.56 (1 H, q, $=CHCH_3$), 6.62–7.06 (5 H, m, Arom). This material was converted to the citrate salt as described above: mp 118–120 °C (from 2-propanol). Anal. ($C_{23}H_{33}NO_{10}$) C, H, N.

Biological Methods. $CaCl_2$-Induced Fibrillations in Anesthetized or Conscious Rats. Fibrillations were induced by a rapid iv injection of 1 mL/kg of an 8% $CaCl_2$ solution into anesthetized (with urethane, 2.8 g/kg sc) or conscious albino Sprague–Dawley rats weighing 180–200 g. The compounds were administered into the caudal and portal veins or orally, respectively, 2 or 60 min before $CaCl_2$. ECG recording from the II lead was continuously performed from shortly after administration of the arrhythmogenic agents until the appearance of fibrillations within 10 min. The heart rate was recorded a few seconds before administration of either the antiarrhythmic or the arrhythmogenic agents only in anesthetized rats. Five to ten animals were tested for each dose of a given compound.

Arrhythmias Induced in Isolated Rabbit Atria by Increasing the Rate of Electrical Stimulation. The atria, quickly removed from New Zealand rabbits sacrificed by cervical dislocation, were suspended in oxygenated Ringer–Locke solution at 29 °C and electrically stimulated with rectangular pulses of 10-ms duration and 10-V voltage at progressively increasing frequencies until the atria failed to follow each stimulus, thus determining the basal maximum driven frequency. The antiarrhythmic activity of the compounds was evaluated by their ability to reduce the maximum rate of electrical stimulation that rabbit atria would follow. Measurements of the maximal atrial following frequency were made prior to and 10, 15, and 20 min after the drugs were added to the bath. Dose–response curves were obtained on the same tissue and repeated at least three to five times.

Aconitine-Induced Arrhythmias in Anesthetized Mice. Albino CF_1 mice of both sexes weighing 20–22 g were anesthetized with pentobarbital (60 mg/kg ip followed by 30 mL/kg sc). The animals were placed on their backs and electrodes fixed in appropriate positions to record ECG from the II lead. The drugs were administered by iv (caudal vein) or oral routes, respectively, 2 and 60 min before the infusion of aconitine was started. In the case of oral administration, the animals were treated 55 min before anesthesia. Aconitine was infused at the rate of 8 μg/mL (equal to 0.32 mL/min) for 3 min, and the ECG was registered every 10 s. The time that elapsed from administration of aconitine to the appearance of both initial arrhythmias and ventricular tachycardia was evaluated. Ten animals were used for each dose of a given compound.

Arrhythmias Induced by Coronary Ligature in Dogs. Beagle dogs of both sexes weighing 10–14 kg were anesthetized with pentobarbital (30 mg/kg iv) and kept under artificial ventilation. Thoracotomy was performed under sterile conditions and the heart exposed. The left descending coronary artery was ligated at about 2 cm from the tip. The wound was sutured and the dog allowed to recover from anesthesia. Later (20–24 h), the conscious animal was equipped with ECG electrodes and tracings were recorded from the II lead.

All dogs not showing spontaneous arrhythmias the day after surgery were treated iv (ear vein) with an arrhythmogenic dose of epinephrine (2–10 μg/kg). In any case, after either the spontaneous or the epinephrine-induced arrhythmias were recorded, the animals received intravenously the most promising antiarrhythmic agents. Their ECGs were registered 5, 15, 30, 60, 90, 120, and 180 min later, and at the same periods they were retreated with epinephrine.

The maximal number of ectopic beats/minute were counted before and after each dose of a given in two to four animals.

Tail-Clip Method in Mice for Local Anesthetic Activity. Albino CF_1 mice of both sexes weighing 18–20 g received an intradermal injection of the tested compounds (0.1 mL/mouse) into the tail at about 1 cm from its root. The anesthetic activity was evaluated 15 min later by placing an arterial clip just on the side of the injection. The animals who did not squeak or try to bite the clip were considered protected.

Acute Toxicity in Mice and Rats. LD_{50} values were determined in albino CF_1 mice and Sprague–Dawley rats of both sexes weighing, respectively, 18–20 and 120–140 g. The mice were treated intraperitoneally and the rats intravenously. The survivors were kept under observation for 1 week. Ten mice were used for each dose of a given compound.

Potassium, sodium, and calcium anions were determined in sera of Sprague–Dawley rats of both sexes, weighing 140–150 g, 1 h after intravenous treatment with the drugs. Potassium and sodium were measured by means of a flame photometric system, and calcium was measured according to the method of Ray Sarker et al.[12] Five rats were used for each dose of a given compound.

Statistical Analyses. ED_{50}, EC_{30}, EC_{50}, and LD_{50} values were calculated according to the probit method,[13] and the confidence limits were reported for $p = 0.05$.

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Registry No. **1a**, 106063-67-6; **1a**·citrate, 106063-68-7; **1b**, 106063-87-0; **1b**·HCl, 106064-03-3; **1c**, 106063-88-1; **1d**, 106063-89-2; **1d**·HCl, 106064-04-4; **1e**, 106063-90-5; **1e**·HCl, 106064-05-5; **1f**, 106063-91-6; **1f** ($CH(CH_3)CH_2$ isomer), 106064-15-7; **1f**·maleate, 106064-06-6; **1g**, 106063-92-7; **1g**·citrate, 106064-07-7; **1h**, 106063-93-8; **1h**·HCl, 106064-08-8; **1i**, 106063-94-9; **1l**, 106063-71-2; **1l**·HCl, 106063-72-3; **1m**, 106063-95-0; **1m**·citrate, 106064-09-9; **1n**, 106063-96-1; **1n**·2maleate, 106064-10-2; **1o**, 106063-97-2; **1o**·citrate, 106064-11-3; **1p**, 106063-98-3; **1p**·tartrate, 106064-12-4; **1q**, 106063-99-4; **1q**·HCl, 106064-13-5; **1r**, 106064-00-0; **1s**, 106063-73-4; **1s**·2maleate, 106063-74-5; **2a**, 106063-69-8; **2a**·citrate, 106063-70-1; **2b**, 106064-01-1; **2b** ($CH(CH_3)CH_2$ isomer), 106064-16-8; **2b**·citrate, 106064-14-6; **2c**, 106064-02-2; **2c**·HBr, 106095-27-6; **3a**, 106063-75-6; **3a**·citrate, 106063-76-7; **3b**, 106063-77-8; **3b**·citrate, 106063-78-9; **3c**, 106063-79-0; **3c**·citrate, 106063-80-3; **3d**, 106063-81-4; **3d**·citrate, 106063-82-5; **3e**, 106063-83-6; **3e**·citrate, 106063-84-7; **3f**, 106095-26-5; **3f**·HCl, 57150-81-9; **3g**, 106063-85-8; **3g**·citrate, 106063-86-9; **4a**, 106063-50-7; **4a**·Na, 106063-49-4; **4b**, 106063-53-0; **4b**·Na, 106063-52-9; **4c**, 106063-51-8; (*Z*,*Z*)-**4d**, 106063-54-1; (*E*,*Z*)-**4d**, 106063-55-2; **5**, 106063-58-5; **5** (acetate), 106063-59-6; **6**, 106063-60-9; **7**, 106063-61-0; **8**, 106063-62-1; **9a**, 106063-63-2; **9b**, 106115-03-1; **9c**, 106063-64-3; **10a**, 106063-65-4; **10b**, 106063-66-5; 11, 57018-15-2; $2\text{-}HOC_6H_4OH$, 120-80-9; (*Z*)-$C_6H_5CH{=}CBrCOCH_3$, 22965-96-4; $4\text{-}HOC_6H_4OCH_2COCH_3$, 13332-74-6; C_6H_5CHO, 100-52-7; $Br(CH_2)_3Br$, 109-64-8; CH_3I, 74-88-4; $C_6H_5CO(CHBr)_2C_6H_5$, 611-91-6; $(C_2H_5)_2N(CH_2)_2Cl$, 100-35-6; $(CH_3)_3CNH_2$, 75-64-9; *c*-$HN(CH_2CH_2)_2NCH_3$, 109-01-3; $2\text{-}HOC_6H_4OCH_2COCH_3$·Na, 5740-96-5; $((CH_3)_2CH)_2N(CH_2)_2Cl$, 96-79-7; *c*-$H_8C_4N(CH_2)_2Cl$, 5050-41-9; *c*-$H_{10}C_5N(CH_2)_2Cl$, 5050-41-9; *c*-$O(CH_2CH_2)_2N(CH_2)_2Cl$, 3240-94-6; $ClCH_2CH(CH_3)N(CH_3)_2$, 53309-35-6; $Cl(CH_2)_3N(CH_3)_2$, 109-54-6; $Cl(CH_2)_3N(C_2H_5)_2$, 104-77-8; $H_3CCHClCH_2N(CH_3)_2$, 108-14-5; *c*-$H_{10}C_5N(CH_2)_3Cl$, 1458-63-5; $((H_3C)_2CH)_2NH$, 108-18-9; 4-chlorocatechol, 2138-22-9; 3-chloro-1,2-epoxypropane, 106-89-8; *trans*-2-acetyl-6(or 7)-chloro-2,3-dihydro-3-phenyl-1,4-benzodioxin, 106063-56-3; (5-chloro-2-phenyl-1,3-benzodioxol-2-yl)propan-2-one, 106063-57-4; 2-acetyl-2,3-dihydro-3-methyl-1,4-benzodioxin, 3523-32-8.

Synthesis and Antiarrhythmic Properties of Novel 3-Selena-7-azabicyclo[3.3.1]nonanes and Derivatives. Single-Crystal X-ray Diffraction Analysis of 7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonan-9-one and 7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonane Hydroperchlorate

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Several members of the heterocyclic family 3-selena-7-azabicyclo[3.3.1]nonane have been synthesized and characterized via IR, ^1H, ^{13}C, ^{15}N, and ^{77}Se NMR spectroscopy and, in some cases, by X-ray diffraction analysis. Select members, namely the hydroperchlorates of the amines, were examined for antiarrhythmic properties in anesthetized dogs in which myocardial infarctions were induced by techniques previously described. In the predrug, or control state, sustained ventricular tachycardia were induced by ventricular paced beats at rates above 300/min. When 7-benzyl-3-selena-7-azabicyclo[3.3.1]nonane hydroperchlorate was administered at 3 and 6 mg/kg, the sustained ventricular tachycardia could no longer be induced. Similar doses of lidocaine, a commonly used antiarrhythmic, caused slowing of the sustained ventricular tachycardia below 300/min but did not abolish their inducibility. In addition, select members of the hydroperchlorates caused a moderate 10–20% increase in mean blood pressure whereas lidocaine caused either no change in or slightly reduced mean blood pressure. Some general conclusions are delineated concerning the structural requirements that appear to be necessary for activity in this family of heterocycles and that have not been reported previously.

In the course of our investigations for new antiarrhythmic properties in 3,7-diheterabicyclo[3.3.1]nonanes and derivatives, several 3-thia-7-azabicyclo[3.3.1]nonanes were synthesized and were found to be active in certain dog models.[1] Since selenium may bioisosterically replace sulfur[2] and since ^{75}Se is radioactive,[3] we reasoned that such Se relatives might have similar antiarrhythmic activity and might offer a vehicle by which they could serve as part of imaging agents to define an infarcted zone in the heart, the latter being a long-term goal. This paper reveals our synthesis of members of **1** and **2** both of which came from methodology starting from the recently prepared 4-selenanone (**3**).[4] Earlier studies[1] had indicated that such reduced amines as **4**, and more often the salts like **5**, showed the most significant antiarrhythmic action and thus these were prepared from **1** and **2**. Antiarrhythmic effectiveness was assessed in dog models and reported in terms of activity as compared with lidocaine as the standard.

Results and Discussion

Chemistry. Ketones **1** were prepared via a Mannich reaction previously outlined[1] but starting with 4-selenanone (**3**).[3] Reduction of the carbonyl groups under Wolff–Kishner conditions gave the corresponding amines

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