95978-37-3; **7**, 95978-38-4; **8**, 17696-11-6; **9**, 90677-38-6; **10**, 95978-39-5; **11**, 95978-40-8; **12**, 95978-41-9; **13**, 95978-42-0; **14**, 95978-43-1; [^{125}I]-**14**, 95978-44-2; **15**, 95978-45-3; **16**, 95978-46-4; **17**, 95978-47-5; **18**, 95978-48-6; [^{123}I]-**18**, 95978-58-8; [^{125}I]-**18**, 95978-59-9; **19**, 95998-63-3; [^{123}I]-**19**, 95978-49-7; [^{125}I]-**19**, 95978-50-0; **20**, 60451-92-5; **21**, 95978-51-1; **22**, 95978-52-2; **23**, 95978-53-3; **24**, 95978-54-4; [^{123}I]-**24**, 95978-60-2; [^{125}I]-**24**, 95978-61-3; **25**, 95978-55-5; [^{123}I]-**25**, 95978-56-6; [^{125}I]-**25**, 95978-57-7; LiC≡CH, 1111-64-4; $(CH_3)_3SiI$, 18089-64-0; CH_2N_2, 334-88-3; $(n\text{-}Bu)_3SnH$, 688-73-3.

Notes

N-Phenylpiperazine Derivatives with Hypocholesterolemic Activity

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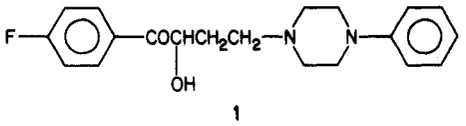
A series of new 4-(4-phenyl-1-piperazinyl)-1-(4-fluorophenyl)-2-(acyloxy)-1-butanones and 4-aryl-5-[ω-(4-aryl-1-piperazinyl)alkyl]-1,3-dioxol-2-ones were synthesized and tested preliminarily for hypolipemic activity. Plasma cholesterol-lowering activity in normal rats was found especially in several dioxolones, two of the most active compounds (**6** and **8**) being more potent than clofibrate. 4-(4-Chlorophenyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one (**8**, LR-19,731) has been selected for clinical trials.

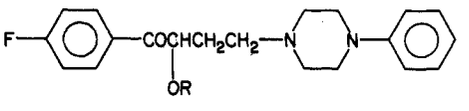
In a preceding paper we reported that α-ketols structurally related to a family of drugs widely used in the therapy of neurodisorders (haloperidol, butropipazone, fluanisone, etc.) are practically devoid of any neuroleptic activity.[1] In spite of this negative result, the research was continued in a different direction, since among the other products ketol **1** was found to possess some interesting hypocholesterolemic properties. Indeed, it was already known that the biosynthesis of cholesterol is to some extent inhibited by some butyrophenones endowed with neuroleptic activity.[2] Moreover, several *N*-phenylpiperazines have been reported to possess hypocholesterolemic activity.[3]



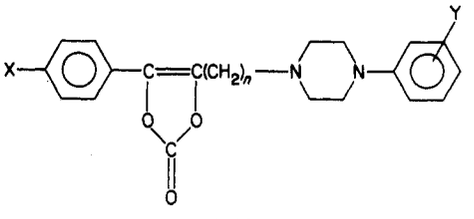
1

In this paper we report the synthesis and some pharmacological data concerning hypocholesterolemic and behavioral activities of a series of new *N*-phenylpiperazines, namely, esters **2–5** and 1,3-dioxol-2-ones **6–20** (listed in Tables I and II, respectively); in the latter, the α-ketol grouping is imbedded in the heterocyclic structure.

Chemistry. Esters **2–3** and **4–5** were obtained by acylation by ketol **1**, respectively, with the corresponding acid chloride or with phosgene in the presence of triethylamine, followed by reaction with the desired amine. The most convenient procedure for the synthesis of 1,3-dioxol-2-one derivatives **6–20** required treatment of the corresponding ketols with phosgene in the presence of triethylamine, followed by thermal cyclization of the intermediate chloroformates (method A). The use of *N,N'*-carbonyldiimidazole in refluxing benzene offered a useful alternative[4] (method B). Dioxolones **7** and **8** were obtained with both procedures.



2-5



6-20

Biological Results and Discussion

All the new compounds were evaluated for activities on rat plasma lipids (cholesterol) and on mouse CNS (spontaneous locomotion). Acute toxicity was tested in mice. 2-(4-Chlorophenoxy)-2-methylpropionate (clofibrate) and 4-(4-phenyl-1-piperazinyl)-1-(4-fluorophenyl)-1-butanone (butropipazone, a neuroleptic chemically related to the new compounds) were included in the biological assays as appropriate standards. The results reported in Tables I and II allow the following observations. The presence of an oxygenated function at the carbon adjacent to the carbonyl group of butropipazone caused a strong depression of the CNS activity both in esters **2–5** and in 1,3-dioxolones **6–20**. On the other hand, hypolipemic activity was shown to be present in a number of compounds, being very pronounced in the cyclic carbonates **6** and **8**. Hypolipemic activity might well be associated with the *N*-phenylpiperazine moiety; thus, in the dioxolone series, a strong depression or complete loss of the activity was found with several open chain, cycloaliphatic, as well as heterocyclic amines. However, also the α-ketol moiety may play an important role. Possibly, certain of the derivatives (**6–20**) undergo hydrolysis in vivo, releasing the α-ketol grouping, such a function being easily oxidizable to α-dicarbonyl compounds. These redox properties may interfere with enzyme systems involved in cholesterol and lipid biosynthesis.[5] Aromatic ring substitution in the *N*-phenylpiperazine

(1) Cascio, G.; Erba, R.; Manghisi, E.; Biazzi, A.; Ferni, G.; Fregnan, G. B. *Farmaco, Ed. Sci.* **1980**, *35*, 605.
(2) Braun, G. A. In "Drugs Affecting Lipid Metabolism"; Holmes, W. L., Carlson, L. A.; Paoletti, R., Eds.; Plenum Press: New York, 1969; p 473.
(3) *Chem. Abstr.* **1977**, *86*, 190010z; *Chem. Abstr.* **1975**, *82*, 93178v; *Chem. Abstr.* **1975**, *83*, 58876v.
(4) Kutney, J. P.; Ratcliffe, A. H. *Synth. Commun.* **1975**, *5*, 47.
(5) Witiak, D. T.; Kokrady, S. S.; Patel, S. T.; Feller, D. R.; Newmann, H. A. I. *J. Med. Chem.* **1982**, *25*, 90–93.

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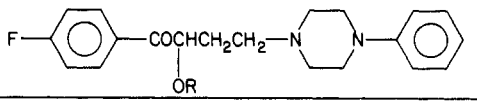
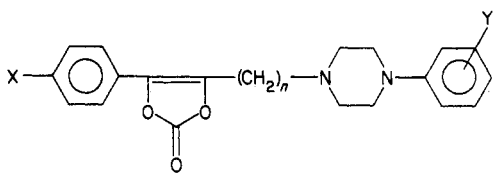
Table I. Physical Properties and Pharmacological Activities of 4-(4-Phenyl-1-piperazinyl)-1-(4-fluorophenyl)-2-(acyloxy)-1-butanones



compd	R	mp,[a] °C	formula	anal.	LD_{50}, mg/kg ip, mice	ED_{50},[b] mg/kg po: rats, cholesterol	ED_{50},[b] mg/kg po: mice, locomotion
1	H	202–203	$C_{20}H_{23}FN_2O_2 \cdot HCl$	C, H, N,	>1000	50	35
2	$COCH_3$	159–160	$C_{22}H_{25}FN_2O_3 \cdot C_4H_4O_4$	C, H, N	575	100	56
3	$COPh\text{-}3,4,5\text{-}(OCH_3)_3$	214–215	$C_{30}H_{33}FN_2O_6 \cdot HCl$	C, H, N	>1000	[100 = 21]	[200 = 13]
4	$CON(CH_3)_2$	208–210	$C_{23}H_{28}FN_3O_3 \cdot 2HCl$	C, H, N, Cl	150	[45 = 35]	30
5	$CONHC(CH_3)_3$	130–133	$C_{25}H_{32}FN_3O_3$	C, H, N	>1000	[200 = 18]	200
butropipazone					95	[100 = 0]	6.5

[a] All compounds were crystallized from EtOH. [b] Dose causing 50% reduction either of plasma cholesterol levels or of spontaneous locomotor activity in normal animals. Numbers in brackets indicate the maximal administered dose and the related percent reduction.

Table II. Physical Properties and Pharmacological Activities of 4-Aryl-5-[ω-(4-aryl-1-piperazinyl)alkyl]-1,3-dioxol-2-ones



compd	X	Y	n	method	mp,[a] °C	formula	anal.	LD_{50}, mg/kg ip, mice	ED_{50},[b] mg/kg po: rats, cholesterol	ED_{50},[b] mg/kg po: mice, locomotion
6	F	H	2	A	264–265	$C_{21}H_{21}FN_2O_3 \cdot 2HCl$	C, H, N, Cl	936	18.6	100
7	H	H	2	A, B	246–248	$C_{21}H_{22}N_2O_3 \cdot 2HCl$	C, H, N, Cl	500	50	50
8	Cl	H	2	A, B	262–265	$C_{21}H_{21}ClN_2O_3 \cdot 2HCl$	C, H, N, Cl	865	11.3	[120 = 31]
9	CH_3	H	2	A	252–254	$C_{22}H_{24}N_2O_3 \cdot HCl$	C, H, N, Cl	>1000	80	[200 = 0]
10	OCH_3	H	2	A	256–258	$C_{22}H_{24}N_2O_4 \cdot 2HCl$	C, H, N, Cl	>1000	[100 = 25]	75
11	SCH_3	H	2	A	254–255	$C_{22}H_{24}N_2O_3S \cdot 2HCl$	C, H, N, Cl	>1000	[100 = 15]	200
12	Ph	H	2	A	242–243	$C_{27}H_{26}N_2O_3 \cdot 2HCl$	C, H, N	>1000	[50 = 0]	[200 = 29]
13	F	$o\text{-}OCH_3$	2	A	238–240	$C_{22}H_{23}FN_2O_4 \cdot 2HCl$	C, H, N	350	[100 = 25]	47
14	F	m-Cl	2	A	200–205	$C_{21}H_{20}ClFN_2O_3 \cdot 2HCl$	C, H, N, Cl	500	[100 = 0]	46
15	Cl	p-Cl	2	A	250–252	$C_{21}H_{20}Cl_2N_2O_3 \cdot HCl$	C, H, N, Cl	>1000	[100 = 8]	[40 = 0]
16	F	$m\text{-}CF_3$	2	A	194–196	$C_{22}H_{20}F_4N_2O_3 \cdot HCl$	C, H, N	1000	[100 = 0]	200
17	F	$3,4\text{-}Cl_2$	2	A	228–230	$C_{21}H_{19}Cl_2FN_2O_3 \cdot HCl$	C, H, N, Cl	600	[100 = 20]	120
18	F	$2,5\text{-}Cl_2$	2	A	240–242	$C_{21}H_{19}Cl_2FN_2O_3 \cdot HCl$	C, H, N, Cl	1000	[100 = 0]	[200 = 0]
19	F	$3,5\text{-}Cl_2$	2	A	277–279	$C_{21}H_{19}Cl_2FN_2O_3 \cdot HCl$	C, H, N, Cl	>1000	[100 = 5]	[100 = 16]
20	F	H	3	A	176–180	$C_{22}H_{23}FN_2O_3 \cdot HCl$	C, H, N		50	[40 = 0]

[a,b] See corresponding footnotes in Table I.

Table III. Plasma Lipid Levels and Liver Weight of Rats after Five Oral Treatments in 4 Days with Clofibrate and Compounds 6 and 8[a]

compd	daily dose, mg/kg po	% plasma lipid reduction: cholesterol total	% plasma lipid reduction: triglycerides	% plasma lipid reduction: phospholipids	% liver wt increase
clofibrate	30	31*	20		3
	100	46*	7	23	21*
	300	43*	(+39)*	(+11)	51*
8	3	16			
	10	48*	15	14	3
	30	72*	22*	58*	13
	100	100*	63*	83*	28*
6	12.5	39*	12	19	9
	25	57*	20	52*	12
	50	76*	36*		12
	100	85*	27*	75*	33*
	300	97*	82*		43*

[a] * = significantly different from control ($p < 0.01$).

moiety reduced (**13**, **17**, **19**) or abolished (**14**, **16**, **18**) the cholesterol-lowering activity. Replacement of the halogen of **6** or **8** with methyl, methoxy, methylthio, or phenyl groups, as well as homologation of the alkyl chain, negatively influenced the hypocholesterolemic activity.

Compounds **6** and **8** were selected for further studies in comparison with clofibrate. The data reported in Table III show that dioxolone derivatives **6** and **8** lowered, in a dose-related manner, plasma total cholesterol more than phospholipids and triglycerides, while no increase of liver weight was observed at the ED_{50} (18.6 and 11.3 mg/kg, respectively). In contrast, clofibrate showed a poor dose–response correlation on cholesterol and did not affect phospholipids; moreover, a significant increase of liver weight was observed at the ED_{50} (about 100 mg/kg), while hypertriglyceridemia appeared at 300 mg/kg.

The data reported in Table IV show that the two dioxolones, as well as clofibrate, practically did not affect liver, ileum, aorta, and skin total cholesterol, a moderate decrease of ileum cholesterol being observed only at 100 mg/kg of **6** and **8**. As for the activity on serum lipoproteins of different density, the data reported in Table IV show that the dioxolones lowered both HDL and LDL cholesterol, being more effective on the LDL fraction at the lowest dose (10 mg/kg). Instead, clofibrate depressed HDL cholesterol, while increasing the LDL. The HDL/LDL ratios might suggest that serum from dioxolone-treated rats contains more HDL antiatherogenic lipoprotein than serum from control or clofibrate-treated rats.

Compound **8** (LR-19,731) was shown to be very effective also in hyperlipemic animals.[6] The mechanism of action of the new dioxolone derivatives is currently under study. Preliminary results suggest that both **6** and **8** do not cause accumulation of desmosterol in plasma and in liver and that their activity is not influenced by the surgical removal of thyroid glands and ovaries. Experiments of general pharmacology also show that they do not affect central and peripheral nervous functions and cardiovascular and respiratory systems and are devoid of any hypothermic, analgesic, antiinflammatory, and skeletal muscle relaxing properties up to a dose of 100 mg/kg.[6] Preliminary clinical trials proved that dioxolone **8** is active in man, producing roughly a 20% decrease in LDL cholesterol and a 8–9% increase in HDL cholesterol after a treatment with a 400-mg daily dose for a month.

Experimental Section

Chemistry. Melting points were determined on a Buchi capillary apparatus and are uncorrected. Analytical results for indicated elements were within ±0.4% of the theoretical values. The IR and UV spectra were obtained on Perkin-Elmer 237 and Beckman DB-GT spectrophotometers. NMR spectra were recorded on a Perkin-Elmer R-24 instrument (Me_4Si internal standard). Only significant spectral data are reported. For purity tests, TLC was performed on silica gel 60 F_{254} plates (Merck) with 5–20% MeOH–$CHCl_3$ as developing solvent. Organic extracts were dried over Na_2SO_4.

1-(4-Fluorophenyl)-2-hydroxy-4-(4-phenyl-1-piperazinyl)-1-butanone hydrochloride (1) was synthesized as previously reported:[1] mp 202–203 °C (EtOH); yield 60%; IR (Nujol) 1690 cm^{-1}; UV (EtOH) λ_{max} 245 nm (ϵ 21 574); NMR ($CDCl_3$ + CD_3OD) δ 8.19 (dd, 2 H, ortho aromatic H), 7.15 (m, 7 H, aromatic H), 5.24 (dd, 1 H, CH), 4.00 (br s, exchangeable, 1 H, OH), 3.20 (m, 4 H, CH_2), 2.60 (m, 6 H, CH_2), 2.05 (m, 2 H, CH_2). Anal. ($C_{20}H_{24}ClFN_2O_2$) C, H, N.

The ketols **7a–20a** used as starting materials for the synthesis of dioxolones **7–20** were prepared in an analogous manner. Their physical properties are listed in Table V.

1-(4-Fluorophenyl)-2-(acetyloxy)-4-(4-phenyl-1-piperazinyl)-1-butanone Maleate (2). A mixture of the free base from **1** (15 g, 0.044 mol), acetyl chloride (6.30 g, 0.08 mol), and dry pyridine (20 mL) was refluxed for 4 h. The solution was evaporated under reduced pressure to a thick oil, which was treated with benzene (500 mL) and washed with saturated $NaHCO_3$ solution and water. After drying, it was filtered and evaporated under reduced pressure to dryness and the oily residue was converted to a crystalline maleate in EtOH. Recrystallization from EtOH afforded 11.9 g (53.8%) of **2**: mp 157–159 °C; IR (Nujol) 1745, 1695 cm^{-1}; UV (EtOH) λ_{max} 247 nm (ϵ 26 600); NMR (CD_3OD) δ 8.30 (dd, 2 H, ortho aromatic H), 5.25 (dd, 1 H, CH), 2.20 (s, 3 H, CH_3). Anal. ($C_{26}H_{29}FN_2O_7$) C, H, N.

Compound **3** was prepared in an analogous manner (yield 61%).

1-(4-Fluorophenyl)-2-[(dimethylcarbamoyl)oxy]-4-(4-phenyl-1-piperazinyl)-1-butanone Dihydrochloride (4). To a 20% solution of phosgene in toluene (17.6 mL, 0.035 mol) cooled

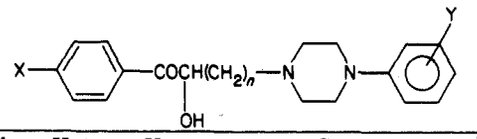
Table IV. Total Cholesterol Levels in Serum, Liver, Ileum, Aorta, and Skin of Rats after Five Oral Treatments in 4 Days with Clofibrate and Compounds **6** and **8**[a] (Serum HDL and LDL Cholesterol Levels Were Also Determined)

		total cholesterol levels										serum				
	daily dose,	serum		liver		ileum		aorta		skin		HDL		LDL		HDL/
compd	mg/kg po	mg	Δ, %	mg	Δ, %	mg	Δ, %	mg	Δ, %	mg	Δ, %	mg	Δ, %	mg	Δ, %	LDL
vehicle		67.4 ± 2.8		277 ± 5		176 ± 4		165 ± 4		131 ± 12		48.7 ± 0.7		18.7 ± 1.5		2.6
clofibrate	100	44.9 ± 2.0*	−33*	251 ± 11	−9	161 ± 6	−8	164 ± 6	−1	115 ± 12	−12	24.8 ± 2.4*	−49*	20.1 ± 2.1	+7	1.2
	300	49.3 ± 1.8*	−27*	240 ± 11	−13	167 ± 7	−5	184 ± 11	+12	182 ± 66	+39	17.1 ± 1.8*	−65*	32.2 ± 2.4*	+72*	0.5
8	10	39.5 ± 2.7*	−41*	287 ± 8	+4	167 ± 12	−5	162 ± 12	−2	100 ± 5	−23	32.4 ± 3.2*	−33*	7.1 ± 1.9*	−62*	4.6
	30	18.7 ± 3.2*	−72*	268 ± 8	−3	159 ± 9	−10	155 ± 4	−6	102 ± 3	−22	12.6 ± 2.5*	−74*	6.1 ± 1.4*	−67*	2.1
	100	3.4 ± 0.7*	−95*	243 ± 6	−12	126 ± 8*	−29*	162 ± 8	−2	107 ± 8	−18	2.1 ± 0.6*	−96*	1.3 ± 0.4*	−93*	1.6
6	10	41.6 ± 2.2*	−38*	270 ± 5	−3	177 ± 2	+1	152 ± 12	−8	106 ± 1	−18	34.0 ± 2.7*	−30*	7.6 ± 1.6*	−59*	4.5
	30	23.4 ± 4.3*	−65*	265 ± 6	−4	167 ± 5	−5	160 ± 3	−3	131 ± 22	0	15.8 ± 3.0*	−68*	7.6 ± 1.8*	−59*	2.1
	100	10.3 ± 4.4*	−85*	255 ± 8	−8	133 ± 6*	−24*	172 ± 11	+6	118 ± 14	−10	6.4 ± 3.7*	−87*	3.9 ± 0.7*	−79*	1.6

[a] * = significantly different from vehicle ($p < 0.05$).

(6) Fregnan, G. B.; Frigerio, L.; Porta, R. *Pharmacology* **1981**, 22, 311.

Table V. 1-Aryl-2-hydroxy-ω-(4-aryl-1-piperazinyl)-1-alkanones



compd	X	Y	n	mp,[a] °C	formula[b]
7a	H	H	2	144–146	$C_{20}H_{24}N_2O_2$
8a	Cl	H	2	150–152	$C_{20}H_{23}ClN_2O_2$
9a	CH_3	H	2	207–208	$C_{21}H_{26}N_2O_2 \cdot HCl$
10a	OCH_3	H	2	137–139	$C_{21}H_{26}N_2O_3$
11a	SCH_3	H	2	155–156	$C_{21}H_{26}N_2O_2S$
12a	Ph	H	2	160–162	$C_{26}H_{28}N_2O_2$
13a	F	o-OCH_3	2	105–106	$C_{21}H_{25}FN_2O_3$
14a	F	m-Cl	2	120–122	$C_{20}H_{22}ClFN_2O_2$
15a	Cl	p-Cl	2	166–168	$C_{20}H_{22}Cl_2N_2O_2$
16a	F	m-CF_3	2	105–107	$C_{21}H_{22}F_4N_2O_2$
17a	F	3,4-Cl_2	2	92–94	$C_{20}H_{21}Cl_2FN_2O_2$
18a	F	2,5-Cl_2	2	92–93	$C_{20}H_{21}Cl_2FN_2O_2$
19a	F	3,5-Cl_2	2	84–85	$C_{20}H_{21}Cl_2FN_2O_2$
20a	F	H	3	182–184	$C_{21}H_{25}FN_2O_2 \cdot HCl$

[a] All compounds were recrystallized from EtOH. [b] All compounds had analyses within ±0.4% for C, H, and N.

to 0 °C and stirred were added in 30 min a solution of the free base from **1** (10 g, 0.029 mol) and triethylamine (3.84 g, 0.038 mol) in dry chloroform (130 mL). The mixture was stirred for 30 min at 0 °C and then left for 5 h at room temperature. A solution of dimethylamine (3.96 g, 0.088 mol) in toluene (20 mL) at 0 °C was added slowly, while the temperature was kept below 10 °C. The mixture was stirred at room temperature for 2 h and then washed with water. The dried solution was evaporated to an oil, which was dissolved in EtOH and converted to its hydrochloride. Recrystallization from EtOH afforded 9.5 g (67.3%) of **4**: mp 208–210 °C; IR (Nujol) 1720, 1695 cm^{-1}; UV (EtOH) λ_{max} 245 nm (ϵ 26 295): NMR ($CDCl_3$) δ 8.02 (dd, 2 H, ortho aromatic H), 5.9 (dd, 1 H, CH), 2.9 (s, 6 H, CH_3). Anal. ($C_{23}H_{30}Cl_2FN_3O_3$) C, H, N, Cl. Compound **5** was prepared in an analogous manner (yield 55%).

General Synthesis of Dioxolones 6–20. Method A. 4-(4-Fluorophenyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride (6) was prepared by an adaptation of the procedure described by Sheehan et al.[7] A solution of the free base from **1** (10 g, 0.029 mol) and triethylamine (7.4 g, 0.073 mol) in dry chloroform (140 mL) was added during 1 h at 0 °C, with stirring, to a 20% solution of phosgene in toluene (43.8 mL, 0.087 mol). The mixture was allowed to warm slowly to room temperature and then refluxed for 6 h. After the mixture cooled, diethyl ether (60 mL) was added. The solid was collected by filtration and washed with H_2O. Dissolution of the solid in ethanol (80 mL), followed by addition of a large excess of gaseous HCl, gave **6** (10 g): mp 264–265 °C; yield 78%; IR (Nujol) 1815 cm^{-1}; UV (EtOH) λ_{max} 250 nm (ϵ 24 785); NMR (CD_3SOCD_3) δ 7.5 (m, 9 H, aromatic H), 3.5 (m, 12 H, CH_2). Anal. ($C_{21}H_{23}Cl_2FN_2O_3$) C, H, N, Cl. With use of the appropriate ketols **7a–20a** as starting materials, dioxolones **7–20** were similarly prepared. Yields varied from 50% to 75%.

Alternative Synthesis of Dioxolones. Method B. 4-Phenyl-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride (7) was synthesized according to Kutney et al.[4] A solution of **7a** (10 g, 0.030 mol) and *N,N'*-carbonyldiimidazole (20 g, 0.12 mol) in dry benzene (400 mL) was refluxed for 8 h. The cooled mixture was washed with water (5 × 200 mL) and dried. Removal of the solvent under reduced pressure left an oil, which was converted to a crystalline dihydrochloride (**7**) in ethanol: mp 246–248 °C; yield 61%; IR (Nujol) 1820 cm^{-1}; UV (EtOH) λ_{max} 245 nm (ϵ 24 100); NMR ($CD_3COCD_3 + D_2O$) δ 7.10 (m, 10 H, aromatic H), 3.30 (m, 12 H, CH_2). Anal. ($C_{21}H_{24}Cl_2N_2O_3$) C, H, N, Cl. Compound **8** was prepared in an analogous manner (yield 59%).

Biological Methods. Hypocholesterolemic activity was evaluated in normal Sprague–Dawley rats (150–200 g of body weight) treated by oral route five times in 4 days (once during the first three days and twice on the fourth day) with the drugs under study. Immediately after the last treatment, the food was withdrawn and 18 h later the blood was collected from the abdominal aorta with the animals under ether anesthesia and plasma or serum fractions were prepared. The liver was removed and weighed as soon as possible. A portion of liver, skin, ileum, and abdominal aorta was dissected. The blood fractions and the names tissues were kept at −20 °c until used for lipid assays.

Total cholesterol and triglyceride plasma levels were determined enzymatically according to the techniques described respectively by Roschlau et al.[8] and by Eggstein.[9] Total cholesterol in tissues was measured by gas chromatography according to Blomhoff.[10] Serum HDL and LDL cholesterol was fractionated as described by Burstein et al.[11] The phospholipids in serum were determined as inorganic phosphorus according to the method illustrated by Varley.[12]

The influence on general behavior was tested in CF_1 mice (20–22 g of body weight), 30 min after an acute oral treatment, by measuring the spontaneous locomotor activity in a Danuso's activity cage during 10 min of observation. Acute toxicity was also evaluated in mice treated intraperitoneally and kept under observation for 15 days.

The drugs were solu-dispersed in an arabic gum suspension of various concentrations in order to administer a constant volume of 5 mL/kg, groups of 5–10 rats being generally treated with the given amount of drug. Groups of animals received the vehicle alone and biochemical, pharmacological, and toxicological tests were performed as well. LD_{50} and ED_{50} values reported were calculated according to Finney,[13] when sufficient data were available. The data reported in Tables III and IV were evaluated with ANOVA and Dunnett's tests, with significant differences ($p < 0.05$) from the control also reported.

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Registry No. **1**, 51037-47-9; **1**·HCl, 95217-21-3; **2**, 51037-61-7; **2**·maleate, 95217-22-4; **3**, 95217-23-5; **3**·HCl, 95217-24-6; **4**, 95248-89-8; **4**·2HCl, 51037-67-3; **5**, 51037-68-4; **6**, 71923-29-0; **6**·2HCl, 71922-95-7; **7**, 71923-51-8; **7**·2HCl, 71923-00-7; **7a**, 51037-52-6; **8**, 71923-34-7; **8**·2HCl, 71923-01-8; **8a**, 51037-53-7; **9**, 71923-36-9; **9**·HCl, 71923-03-0; **9a**·HCl, 95217-25-7; **10**, 71923-43-8; **10**·2HCl, 77606-24-7; **10a**, 51037-54-8; **11**, 71923-44-9; **11**·2HCl, 71923-10-9; **11a**, 95217-26-8; **12**, 71923-47-2; **12**·2HCl, 71923-21-2; **12a**, 95217-27-9; **13**, 95217-28-0; **13**·2HCl, 95217-29-1; **13a**, 51037-51-5; **14**, 71923-49-4; **14**·2HCl, 71923-24-5; **14a**, 95217-30-4; **15**, 71923-52-9; **15**·HCl, 71923-16-5; **15a**, 95217-31-5; **16**, 71923-48-3; **16**·HCl, 71923-23-4; **16a**, 95217-32-6; **17**, 71923-40-5; **17**·HCl, 71923-07-4; **17a**, 95217-33-7; **18**, 77606-27-0; **18**·HCl, 71923-06-3; **18a**, 95217-34-8; **19**, 71923-38-1; **19**·HCl, 71923-04-1; **19a**, 95217-35-9; **20**, 71923-50-7; **20**·HCl, 71923-15-4; **20a**·HCl, 95217-36-0.

Supplementary Material Available: Table VI listing physical properties and hypocholesterolemic and toxicity screening data for 10 miscellaneous 5-(aminoethyl)-4-(4-halophenyl)-1,3-dioxol-2-ones (1 page). Ordering information is given on any current masthead page.

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