Blood Glucose Lowering Sulfonamides with Asymmetric Carbon Atoms. 2[†]

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In continuation of our work on new antidiabetic drugs with asymmetric carbon atoms, a number of chiral sulfonylureas and -aminopyrimidines were synthesized and pharmacologically evaluated. Some of the new compounds exhibit excellent hypoglycemic activity. The influence of absolute configuration as well as structural features upon the activity within this series is discussed.

As was shown recently² sulfonylaminopyrimidines of the type represented by formula 22 (Table I) belong to the most effective hypoglycemic drugs since they cause blood sugar decrease in man at doses of about 0.1 mg/kg. In rabbits 22 is active at less than 1 mg/kg and therefore was chosen to serve as a standard for further investigations on new antidiabetic compounds.

In the preceding paper¹ we could demonstrate the remarkable increase of hypoglycemic activity if the unsubstituted anilide part of the sulfonylaminopyrimidine 1 is replaced by a benzylamide (2) or an α -alkylbenzylamide moiety (3). Furthermore, it was shown that the configuration of the asymmetric center as well as size and type of the attached substituent at C^{*} (3) determines the hypoglycemic activity of the whole molecule. This led to the hypothesis of a second binding site at the unknown receptor.



^aSee footnote a, Table I.

The present paper now deals with the question of whether there are similar dramatical changes in activity to be observed when the achiral, but highly active type of compounds 4 (e.g., compounds 20 and 21, see Table I) is transformed into a chiral one by specific modifications. The results of this investigation are summarized in Table I.



Chemistry. The compounds listed in Table I were synthesized following well-known procedures.[‡] The pathways are outlined below.



 $\mathbf{R}_1 = \mathbf{pyrimidine}$

† For the previous paper in this series, see ref 1.

[‡] Starting materials or intermediates are described in the Experimental Section.

Method A. An acyl chloride [(a), racemic or optically active] is allowed to react with an amine in the presence of a base (e.g., Et₃N). The amine part (b) can be prepared in a fashion analogous to procedures described.³

Method B. Most of the compounds were prepared following methods B. The sulfonylaminopyrimidines (f) are synthesized by reaction of a sulfonyl chloride (d) with an aminopyrimidine (e) in the presence of a suitable base like pyridine or Et₃N or with an excess of (e). The sulfonylureas (h) are prepared by reaction of the sulfonamides (g) with an appropriate isocyanate in the presence of K₂CO₃. The sulfonylsemicarbazide (k) (compound 13, Table I) is obtained following route B_3 by reaction of the sulfonylurethane (i) with 1-aminoperhydroazepine in absolute glyme. The intermediate chlorosulfonyl product (d) can be prepared by direct chlorosulfonation with ClSO₃H (see Experimental Section). In the case of compound 15 (Table I) the direct chlorosulfonation gave an intractable mixture of products. Therefore, the overall yield of the desired product was very low.

Results and Discussion

Compound 8 (Table I) is formally derived from glibenclamide (20), one of the most active antidiabetic drugs, by introduction of a Me substituent into the α position of the phenethylamine part (amphetamine-like structure), thus generating a chiral molecule with decreased hypoglycemic activity. No significant difference in hypoglycemic activity between the two pure enantiomers is noticed. The same result is observed with the enantiomeric sulfonylaminopyrimidines 7 which are as active as the sulfonylureas 8. In 9, the aromatic ring (5-chloro-2-methoxybenzene) is replaced by a heteroaromatic ring (5-methylisoxazole) which is also present in another very potent antidiabetic compound (21, glisoxepide, BS 42314). However, since the activity of 9 is poor, we did not prepare the enantiomers. If the β position of the phenethylamine part possesses asymmetry (as in compound 12), the activity is also decreased and no differences in activity between racemic 12 and its stereoisomers are to be observed. The sulfonylsemicarbazide 13 (1 mg/kg) is slightly more active than the sulfonylurea 12 (3 mg/kg).

By contrast with the sulfonylureas 12 and the sulfonylsemicarbazide 13 the corresponding sulfonylpyrimidines 10 and 11 have increased hypoglycemic activity. This effect is surprising since the achiral sulfonylureas of type 20, in general, are a little more active than the corresponding sulfonylpyrimidines.^{5a,b} Again, no significant difference in activity between the R and S isomer can be recognized. If both, α and β position, of the phenethylamine part are substituted by Me, as in 14, blood sugar lowering activity disappears (compare with 11). Modification of the aryl part A of the general formula 4 led to compounds 5 and 6 which consist of the chiral α -methylbenzyl group instead of the 5-chloro-2-methoxyphenyl substituent. By this variation the activity is decreased. The observed difference in activity between the enantiomers (R)-5 and (S)-5 is doubtful. The R isomer seems to be



more active than the S isomer. This is in contrast to the former series of compounds¹ in which the S isomer [e.g., (S)-22 (0.1 mg/kg)] was much more active than the R isomer [(R)-22 (30 mg/kg)].



In the preceding paper¹ it was concluded that the distance d between the amide nitrogen and the sulfonamide nitrogen (Table I, 20-22) is crucial for hypoglycemic activity. This is supported by examples reported⁵ as well as by results obtained in our laboratories.^{1,2} It was found that a 2-carbon chain between the amide nitrogen and the phenylene ring is a presupposition for optimum activity, regardless as to whether the compounds belong to type 20 or type 22. Compound 16 (Table I) provides further evidence for this finding. Part B contains an asymmetric 1carbon link; therefore, reduced activity is expected and found. However, the influence of the same link B on the sulfonylaminopyrimidine 15 (1 mg/kg) is not as pronounced as on the sulfonylurea 16 (30 mg/kg). No difference in activity is found for the enantiomers of these compounds.

The more surprising are the pharmacological data of compounds 17 and 18 which contain the same asymmetric term B as compounds 15 and 16. The hypoglycemic activity of the R antipodes is excellent and differs remarkably from that of the S stereoisomers. In fact, (R)-18 belongs to the most active hypoglycemic compounds with an effective dose of 0.1 mg/kg. Compound 19 with its bulkier alkyl substituent in part B is less active, thus indicating extreme sensitivity of this type of compounds to structural modifications.

Although we do not fully understand the different data of compounds 17-19 in comparison with compounds 15 and 16, we feel that the isoxazole ring plays a peculiar role in the hypoglycemic action of these substances different from that of the benzene nucleus (5-chloro-2-methoxyphenyl ring). Perhaps the isoxazole nitrogen may compete with the amide nitrogen at the receptor or is bound to another receptor site if the molecule is of proper configuration.

In summary, we conclude the following on the basis of this investigation. 1. Introduction of an asymmetric term A or B into compounds of type 4 (Table I, acylaminoalkylbenzenesulfonamide series), in general, does not lead to compounds with improved hypoglycemic activity, compared to the parent compound. 2. The only exceptions obtained so far are the compounds in which the asymmetric link B is represented by $-CH(CH_3)$ - in connection with an isoxazole ring for term A (see compounds 17 and 18). In these cases the R antipodes exhibit superior activity to the S isomers.

Experimental Section

General. Melting points were determined in open capillary tubes and are uncorrected. Analytical data of the compounds listed in Table I were obtained at least for N and S and were within $\pm 0.4\%$ of the calculated values, unless otherwise stated. Analytical data of the compounds not listed in Table I were indicated by symbols of elements if they were within $\pm 0.4\%$ of the theoretical values. Additionally, most of the compounds have been structurally confirmed by ir, nmr, or uv spectra, the details of which are not given. All reactions were controlled by tlc. Starting materials or intermediates not mentioned in this part were commercially available or prepared according to the literature.

 β -Methylphenethylamine (23).⁶ To a solution of 100 g of α methylphenylacetonitrile in 500 ml of MeOH was added 10 g of Raney Ni (washed with EtOH before addition) and the suspension was saturated with NH₃ at 0°. The mixture was hydrogenated in an autoclave at 100° and 90 atm (with shaking) for 2 hr when hydrogen uptake stopped. After filtration, evaporation of the solvent, and distillation 90 g (86%) of 23 was obtained: bp 44-46° (0.4 mm); (glc 98%); nmr as expected. 23-HCl had mp 124°.

The resolution^{7,8} of compound 23 was simply accomplished by the following procedure. β -Methylphenethylamine (1 mol) was added to a hot solution of 1 mol of (+)-tartaric acid in 2 l. of MeOH and the mixture was allowed to cool and stand for 5 hr. The precipitating crystals were collected and recrystallized three times from MeOH using 10 ml of solvent for 1 g of diastereomeric tartrate. The last crop was dissolved in water and the amine liberated by addition of excess NaOH. The amine was extracted with Et₂O-benzene; the organic layer was filtered and evaporated. Finally the amine was distilled *in vacuo* to yield 34% of (*R*)-23: bp 85° (11 mm); $[\alpha]^{20}$ D +34° [(c 1 (EtOH); 97.5% optical purity)].§

The mother liquor of the first crystallization was evaporated and the residue treated with NaOH. The liberated base was extracted with Et₂O-benzene and after evaporation treated with (-)-tartaric acid. The tartrate was collected and three times recrystallized from MeOH. Liberation of the amine and distillation afforded 28% of (S)-23: $[\alpha]^{20}D$ -33° [c 1 (EtOH); optical purity 96%].§

 α_{s} -Dimethylphenethylamine (24) was prepared according to ref 10: yield 40%; bp 95-97° (12 mm).

5-Chloro-2-methoxy- $N \cdot (\beta$ -methylphenethyl)benzamide (25). 5-Chloro-2-methoxybenzoyl chloride (11.3 g, 0.055 mol) was added

[§] Optical purity was calculated from the literature value.⁷ The recently published method⁹ (determination of optical purity and absolute configuration by means of nmr of the diastereometic camphor sulfonamides) is not applicable to amines of the β -alkylphenethylamine type.

	Dose,ª mg/kg	30 30 30	30		က က	30	$egin{array}{c} 0.25\ 0.5 << 1 \end{array}$	$\begin{array}{c} 0.5\\ 0.25\end{array}$	ကို ကိ	3,6	$\mathbb{1}^{k}$
	$^{M_{D,}^{\circ}}_{ m C}$	126 126 126	136	138 138	200 200		178 163 162	$133 \\ 133$	$156 \\ 157, \\265^{h}$	264	166
	Crystn solvent	MeOH MeOH-H₂O	MeOH-H ₂ O	MeOH MeOH	MeOH MeOH		EtOAc MeOH MeOH	MeOH MeOH	<i>i</i> -PrOH MeOH	MeOH	MeCN
	Yield, ⁴ $\%$	38 54 48	32	27 28	53 33		40 44 25	$\frac{15}{13}$	53 69	46	28
	Method	AAA	A	B _I	B B	••	ũ ữ ữ	щщ	\mathbf{B}_{2}^{n}	\mathbf{B}_2	B_3
٥Ĩ	$[\alpha]^{20}$ D, deg	+4.2 -4.1 (c 1, CHCl ₃)		+24 - 23 (c 0.5, EtOH	$^{-4.0}_{+4.6(c0.5,$		+55.2 -55.0 (c 1, EtOH)	+50.2 -50.2 (c 0.5, EtOH)	+55.5	-54.7 (c 1, EtOH)	
	Confign at C*	R,S S S	R,S	R	S PS	R,S	R,S S	R S	R,S R	S	R,S
ACONHB-	${f Formula}$	$\mathrm{C}_{24}\mathrm{H}_{28}\mathrm{N}_4\mathrm{O}_4\mathrm{S}$	$C_{25}H_{30}N_4O_3S$	C25H29CIN404S	$C_2, H_{30}CIN_3O_5S$	$C_{22}H_{30}N_4O_5S$	C ₂₅ H ₂ ,CIN ₄ O ₄ S	C ₂₄ H ₂₇ ClN4O ₅ S	C ₃ ,H _M CIN ₃ O,S·H ₂ O/		$C_{34}H_{31}CIN_4O_5S$
	\mathbf{R}_{i}	Not the second s		CH3 NO-CH4CH CH3		-CONH-	-NO-CHICH CH3	N OCH CH3	O O		- CONHN
	В	-jHj.h)-	-CH ^T CH ^T -	CH ₃ -CHCH ₂ -	СН ₃ -СНСН ₂ -	сн _。 - - снсн -	СН, -СН,СН-	CH₄ + -CH₂CH-	CH.	- HIVII-)-	сн, + -(Н,СН-
	¥	H-+		UCH C	U U U U U U U U U U U U U U U U U U U	H,C,N,N,H,C,N,N,N,N,N,N,N,N,N,N,N,N,N,N,	OCH.		C (CH)	OCH3	octic
	Compd	хœ	9	м	œ	6	10	11	61	77	13

Table I. Hypoglycemic Sulfonamides

14	ocH ₃	СН, СН, СН, - С. С. - С С. - Н*	N OCH CH3	C25H29CIN405S	R,S; R,S		\mathbf{B}_{I}	40	EtOH-pet. ether	143	30
1	- -	°Hı	N CH ³		R	-23.4	$\mathbf{B}_{\mathbf{I}}$	5	<i>i</i> -PrOH-	110	1
15	OCH3	-CH-	N C C C C C C C C C C C C C C C C C C C	C24H27CIN4O4S	S	$+23.2 (c 0.5, CHCl_3)$	\mathbf{B}_{I}	4	cyclohexane <i>i</i> -PrOH– cyclohexane	110	1
16	CCH CC	CH ₃ -t [*] CH ₃	CONH	C ₃₃ H ₂₈ CIN ₃ O ₅ S	a s	+1.4 -1.5 (c 1, MeOH)	B B	44 61	MeOH EtOH	183 182	30 30
17	H CON NON	CH- -CH-	HN00) -	C20H26N4O.S	R,S S	+32.4 -32.0 (c 1, MeOH)	$\mathbf{B}_{\mathbf{z}}^{\mathbf{z}_{i}}$	75 44 82	EtOH EtOH EtOH	176 192 193	0.5 0.25 30
18	H _c C H	GH- −CH-	- cont - CH ₃	C21H28N405S	R,S R S	+34.0 -33.5(c0.5,	.~ ₽ ₽	74 70	EtOH EtOH	192 220 220	$\begin{array}{c} 0.25\\ 0.1\\ 30\end{array}$
19	H,C,O,N,H	с,H, -с,H.	- CONH	$C_{21}H_{28}N_sO_sS$	R,S	(HU9M	. 1			194	30
20	CONHCH-	-cH	HNOONH	C ₂₃ H ₂₈ CIN ₃ O ₅ S			L				0.25
21	¹ ¹ ¹ C 0 ^{-N}	g,ltbencl'amide —CHS0_	, which which which we have a second se	C ₂₀ H ₂₈ N ₅ O ₅ S			¥				0.5
22	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	elisoxepide -CHCHSOSO_standard	NH - OCH(CH ₃),	C ₂₂ H ₂₃ CIN,O ₅ S			1				-
^a Lowe 0.5, 0. icrosus	st dose causing a 25, 0.1, and 0.05 pension. Uncorre	blood glucose mg/kg. Unless ected. ^d None o	decrease (fasting rabbi s otherwise stated the c f the reactions were ru	ts, po) which is not sign compounds were applied in to optimum yield. $^{\circ}(K)$	ufficantly different d in aqueous soluti ()-11: Anal. C, H,	from that effected on (sodium salt).] Cl, N; S: calcd, 6 U N: S: calcd, 6	by 1 mg/ For deta 1.18; four	/kg of st ils see tl ad, 7.04	andard 22. The dos the Experimental Sec (S)-11: Anal. N;	e gradatio tion. ^b Adn S: found, 6	in was 30, 3, initiated in (R,S) - $($

to a stirred solution of 14.9 g (0.11 mol) of 23 in 120 ml of absolute CHCl₃. Stirring was continued for 1 hr at room temperature and for 2 hr at 60°. Then the solvent was evaporated and the residue redissolved in CCl₄, washed with water, dried over MgSO₄, and concentrated to yield 13.9 g of (R,S)-25: 83%; mp 87° (cyclohexane).# Anal. (C₁₇H₁₈ClNO₂) C, H, Cl, N. (R)-25 gave a yield of 77%; mp 109° (CCl₄); $[\alpha]^{20}$ D +43.3° (c 1, EtOH). Anal. C, H, Cl, EtOH).

Compounds 26 and 27 were prepared in a similar way. 5-Chloro-2-methoxy-N-(α -methylphenethyl)benzamide (26).** (R)-26 gave a yield of 84%; mp 119° (CCl₄); [α]²⁰D -35.0° (c 1, EtOH). Anal. (C₁₇H₁₈ClNO₂) C, Cl, N; H: calcd, 6.0; found, 6.5. (S)-26 gave a yield of 79%; mp 119° (CCl₄); [α]²⁰D +34.8° (c 1, EtOH). Anal. (C₁₇H₁₈ClNO₂) C, H, Cl, N.

5-Chloro-2-methoxy-N-(α-methylbenzyl)benzamide (27). (R)-27 gave a yield of 94%; mp 95° (CCl₄); $[α]^{20}b$ +18.0° (c 1, CHCl₃). Anal. (C₁₆H₁₆ClNO₂) C, H, Cl, N. (S)-27 gave a yield of 75%; mp 94° (CCl₄); $[α]^{20}b$ -17.5° (c 1, CHCl₃).

4-[2-(5-Chloro-2-methoxybenzamido)-1-methylethyl]benzenesulfonyl Chloride (28). Chlorosulfonic acid (37.3 g, 0.32 mol) was dropwise added to a cooled and stirred solution of 12.2 g (0.04 mol) of (R, S)-25 in 100 ml of CHCl₃. Stirring was continued for 4 hr at room temperature; then the mixture was poured onto 1 l. of ice-water. The organic layer was separated and the aqueous layer extracted with CHCl₃. The combined organic phase was dried over MgSO₄ and the solvent evaporated; on standing (R, S)-28 solidified to yield 13.9 g (86.4%), mp 111°. (R)-28 gave a yield of 95%; mp 110°; $[\alpha]^{20}$ D +81° (c 1, CHCl₃). (S)-28 gave a yield of 90%; mp 110°; $[\alpha]^{20}$ D -80.4° (c 1, CHCl₃).

Compound 29 was prepared in a similar way. 4-[2-(5-Chloro-2-methoxybenzamido)-2-methylethyl]benzenesulfonyl Chloride (29). (R)-29 gave a yield of 83%; mp 85°. (S)-29 gave a yield of 75%; mp 86°.

5-Chloro-2-methoxy-N-(β -methyl-4-sulfamoylphenethyl)benzamide (30). (R, S)-28 (8.8 g, 0.022 mol) was suspended in 80 ml of 25% NH₄OH and the mixture was stirred at room temperature for 5 hr. Subsequently the mixture was diluted with 100 ml of H₂O and neutralized with HCl, and the crystalline material was recrystallized from MeCN to yield (R, S)-30: 6.9 g (82%); mp 156°. (R)-30 gave a yield of 65%; mp 155°; [α]²⁰D +71.5° (c 0.25, EtOH). (S)-30 gave a yield of 73%; mp 155°; [α]²⁰D -72.1° (c 0.25, EtOH). Anal. (C₁₇H₁₉ClN₂O₄S) C, H, Cl, N, S.

Compounds 31 and 32 were prepared in a similar way. 5-Chloro-2-methoxy-N-(α -methyl-4-sulfamoylphenethyl)benzamide (31). (R)-31 gave a yield of 85%; mp 134° (MeOH); [α]²⁰D +35° (c 0.5, EtOH). (S)-31 gave a yield of 87.5%; mp 133° (MeOH); [α]²⁰D -34.5° (c 0.5, EtOH). Anal. ($C_{17}H_{19}ClN_2O_4S$) C, H, Cl, N, S.

5-Chloro-2-methoxy-*N*-(*α*-**methyl-4-sulfamoylbenzyl)benza**mide (32). (*R*)-32 gave a yield of 25%; mp 181° (EtOH); $[α]^{20}$ D +3.7° (*c* 1, MeOH). *Anal.* (C₁₆H₁₇ClN₂O₄S) C, H, Cl, N, S. (*S*)-32 gave a yield of 32%; mp 180° (EtOH); $[α]^{20}$ D -3.7° (*c* 1, MeOH). *Anal.* N, S.

Compound 33 was prepared analogously to ref 11 from 4-(1-aminoethyl)benzenesulfonamide. 5-Methyl-N-(α -methyl-4-sulfamoylbenzyl)isoxazole-3-carboxamide (33). (*R*)-33 gave a yield of 68%; mp 194°; [α]²⁰D +19.8° (c 2, MeOH). (*S*)-33 gave a yield of 80%; mp 195°; [α]²⁰D -20.0° (c 2, MeOH). Anal. (C₁₃H₁₅N₃O₄S) N, S.

Sulfonamides of Table I (5-19). General Procedures. Method A. N-[4-(5-Isopropoxy-2-pyrimidinylsulfamoyl)phenethyl]-2phenylpropionamide (5). Hydratropoyl chloride [prepared from 1.5 g (10 mmol) of hydratropic acid and SOCl₂ in absolute CHCl₃] dissolved in 20 ml of CHCl₃ was added to 3.36 g (10 mmol) of 4-(2-aminoethyl)-N-(5-isopropoxy-2-pyrimidinyl)benzenesulfonamide³ in 200 ml of CHCl₃ and 2 ml of Et₃N. After stirring at room temperature for 40 hr the solvent was evaporated and the residue treated with 20 ml of MeOH. Again the solvent was evaporated and the solid suspended in 100 ml of HCl (3%) for 15 min with stirring; then the solid was collected and recrystallized from a mixture of 80 ml of MeOH and 10 ml of water: yield 1.8 g (38.1%); mp 126°. Analogously prepared were (*R*)-5, (*S*)-5,†† and (*R*,*S*)-6.

Method B₁. 5-Chloro-2-methoxy-N-[4-(5-isobutyl-2-pyrimi-

 \pm Excessive amine was regained from the aqueous layer by addition of NaOH, extraction, and distillation.

**(R)- and (S)- amphetamine were purchased from Aldrich Chemical Co.

†† The resolution of (±)-hydratropic acid was performed according to the literature. 12

dinylsulfamoyl)- β -methylphenethyl]benzamide (10). (R,S)-28 (3 g, 7.5 mmol) was added with stirring to 1.3 g (8.3 mmol) of 2amino-5-isobutylpyrimidine dissolved in 5 ml of pyridine at room temperature; subsequently the mixture was heated at 60° for 3 hr. On cooling and standing for 8 hr the reaction product crystallized. The crystals were collected, dissolved in EtOAc, and washed with dilute HCl and subsequently with NaHCO₃ solution. The organic phase was dried over MgSO₄ and concentrated. The residue was recrystallized twice from MeOH to yield 10: 1.7 g (44%); mp 177°.

Method B₂. 5-Chloro-N-[4-(3-cyclohexylureidosulfonyl)- β methylphenethyl]-2-methoxybenzamide (12). Powdered K₂CO₃ (2.5 g, 0.018 mol) was added to a suspension of 2.3 g (0.006 mol) of (R, S)-30 in 40 ml of Me₂CO and the mixture refluxed for 1 hr. After addition of 0.9 g (0.0072 mol) of cyclohexyl isocyanate heating was continued for about 4 hr. The precipitate was filtered under suction, washed with Me₂CO, and suspended in 2 N HCl. Washing with water and recrystallization from *i*-PrOH and subsequently MeOH afforded (R, S)-12: 1.7 g (53%); mp 156° (MeOH). (R)-12 gave a yield of 69%; mp 157° (*i*-PrOH); mp 265° (MeOH). (S)-12 gave a yield of 46%; mp 264° (MeOH). The nmr spectra of the differently melting products were identical.

Method B₃. Ethyl N-[4-[2-(5-Chloro-2-methoxybenzamido)-1-methylethyl]phenylsulfonyl]carbamate (34). Powdered K_2CO_3 (1.8 g, 13 mmol) was added to 2.5 g (6.5 mmol) of (R,S)-30 dissolved in 50 ml of Me₂CO and the mixture was refluxed for 1 hr and afterward cooled to 20°. Subsequently 1.1 g (10 mmol) of ethyl chloroformate was added and stirring continued for 30 min at room temperature; then the mixture was refluxed for 4 hr. After filtration under suction the precipitate was washed with Me₂CO, then dissolved in water, and precipitated with 2 N HCl. The solid was collected, washed, and dried. Recrystallization from *i*-PrOH afforded 34: 2.5 g (80%); mp 165°. Anal. (C₂₀H₂₃ClN₂O₆S) C, H, Cl, N, S.

5-Chloro-N-[4-(1,1-hexamethylene-4-semicarbazidosulfonyl)- β -methylphenethyl]-2-methoxybenzamide (13). A solution of 1.48 g (0.011 mol) of 1-aminoperhydroazepine (90%) in 5 ml of absolute glyme was dropped at room temperature into a mixture of 4.55 g (0.01 mol) of 34 in 50 ml of glyme. The mixture was refluxed for 3 hr, the solvent was evaporated, and the residue was dissolved in CHCl₃ and washed first with 100 ml of water containing 1 ml of 35% HCl and subsequently with 50 ml of water. The CHCl₃ layer was separated and dried over MgSO₄. Evaporation and recrystallization from MeCN afforded 1.5 g (28%) of 13.

Pharmacological Methods. The biological tests were carried out on groups of six rabbits (male, 24 hr fasted, body weight 2-4 kg). The test compounds were given orally (by gavage) as a sodium salt solution (or microsuspension when indicated). The total volume was 1 ml/kg. The control animals obtained an equal volume of physiological NaCl solution. When the test compound was administered as a microsuspension, the control animals received suspension vehicle (myrg 53). The test compounds were applied in doses of 30, 3, 1, 0.5, 0.25, and 0.1 mg/kg until the blood glucose level was significantly higher than that caused by 1 mg/kg of standard 22. Blood samples were taken from the marginal vein of the ear before treatment and 1, 2, 4, and 6 hr thereafter. The blood glucose content was determined enzymatically by the glucose-oxidase-perid method¹³ in the "Braun-Systematik" autoanalyzer. From the observed blood glucose minima during the test period central values have been calculated and registered. The statistical evaluation of the results utilized the U test¹⁴ ($p \leq$ 0.05

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Hypolipidemic Substituted 1,3-Benzodioxole-2-carboxylates

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Ethyl 5-(4-fluoro- α, α -dimethylbenzyl)-1,3-benzodioxole-2-carboxylate (11, RMI 14,676) was found to be a potent hypolipidemic agent, while ethyl 5-(1-phenyl-1-cyclopentyl)-1,3-benzodioxole-2-carboxylate (19, RMI 14,654), although less potent, was found to show only minimal hepatomegaly in young rats. The two compounds were selected from a series of substituted 1,3-benzodioxole-2-carboxylates and represent a novel type of cyclic analog of clofibrate with structural relationship also to treloxinate. Particular emphasis was given to attempt separation of hypolipidemic activity from hepatomegaly by minor structural modification.

A number of investigations have been concerned with synthesizing and evaluating cyclic analogs of the hypolipidemic agent clofibrate [ethyl 2-methyl-2-(4-chlorophenoxy)propionate, I]. Thus, Witiak and coworkers¹⁻⁴ synthesized ethyl 6-chlorochroman-2-carboxylates II and III, 5chloro-2,3-dihydro-2-benzofurancarboxylate IV, and 1,4benzodioxane-2-carboxylate V. They found that II, IV, and V reduced serum cholesterol and triglycerides in Triton-induced hyperlipemic rats.⁴ From our laboratories⁵ we reported evaluation of hypolipidemic activity in rats of compounds VI and VII of which 5-chloroindole-2-carboxylic acid VII was found to be twice as potent as I in lowering serum cholesterol. We now wish to report on a series of substituted 1,3-benzodioxole-2-carboxylates VIII. These compounds, in addition to their structural relationship to clofibrate I, also share with 1-methyl-4-piperidyl 2,2bis(p-chlorophenoxy)acetate (lifibrate, IX)⁶ and methyl 2,10-dichloro-12H-dibenzo[d,g][1,3]dioxocin-6-carboxylate



(treloxinate, X)⁷ the property of containing an α, α -dioxy-acetate moiety, which may be responsible for some of the advantages that these agents possess over clofibrate.⁸

Clofibrate and treloxinate cause liver hypertrophy in young rats. This phenomenon has been studied extensively with hepatotoxins, enzyme inducers and other chemicals in general, and with clofibrate and clofibrate analogs in particular.⁹⁻¹⁵ Goldberg⁹ advanced the hypothesis that in certain instances, liver enlargement should be considered as an adaptive, functional response of the liver to an increased work load. On the other hand, it is well known that many agents cause liver hypertrophy without affecting serum lipids, while others lower serum cholesterol and triglycerides without causing hepatomegaly.¹⁵ It therefore seemed reasonable to hypothesize that hypolipidemia and hepatomegaly are two separate pharmacological responses to clofibrate-like agents and that it might be possible to separate these two properties by structural 1,3-benzodioxole-2-carboxylates modification. Since showed good hypolipidemic properties, we set out to study this possibility.

Chemistry. Preparation of the parent compound, ethyl 1,3-benzodioxole-2-carboxylate,¹⁶⁻¹⁸ and its 5-chloro derivative^{18,19} has been reported in low yields. We now have developed a preparative method, analogous to that employed for preparation of 12H-dibenzo[d,g][1,3]-dioxocin-6-carboxylate derivatives,⁷ shown in Scheme I. Yields of up to 71% of pure substituted 1,3-benzodioxole-2-carboxylates were obtained, as shown in Table I. Examples are given in the Experimental Section.

Scheme I



The substituted 1,2-benzenediols required were synthesized by known methods and are listed in Table II. The phenoxy-substituted 1,2-benzenediols 22-27 were prepared by Ullmann reaction, followed by ether cleavage as shown in Scheme II, by a procedure described by Mayer and coworkers.²⁰ The phenylalkyl-, phenylcycloalkyl-, and in-