Blood Glucose Lowering Sulfonamides with Asymmetric Carbon Atoms. 2†

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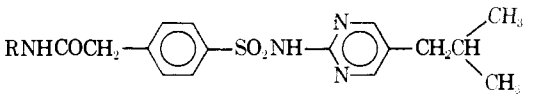
In continuation of our work on new antidiabetic drugs with asymmetric carbon atoms, a number of chiral sulfonylureas and -aminopyrimidines were synthesized and pharmacologically evaluated. Some of the new compounds exhibit excellent hypoglycemic activity. The influence of absolute configuration as well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

As was shown recently[2] 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.

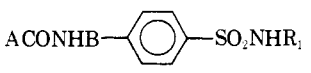
In the preceding paper[1] we could demonstrate the remarkable increase of hypoglycemic activity if the unsubstituted anilide part of the sulfonylaminopyrimidine **1** is replaced by a benzylamide (**2**) or an α-alkylbenzylamide moiety (**3**). Furthermore, it was shown that the configuration of the 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.



	dose,[a] mg/kg
1. R = C_6H_5-	30
2. R = $C_6H_5CH_2$-	0.5
3. R = (±)$C_6H_5CH(CH_3)$-	0.25

[a] See 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.



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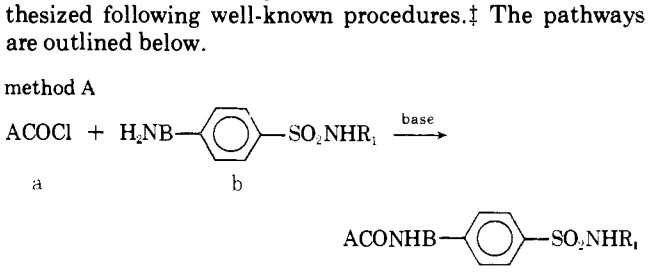
Chemistry. The compounds listed in Table I were synthesized following well-known procedures.‡ The pathways are outlined below.

method A



R$_1$ = 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.*, Et_3N). The amine part (b) can be prepared in a fashion analogous to procedures described.[3]

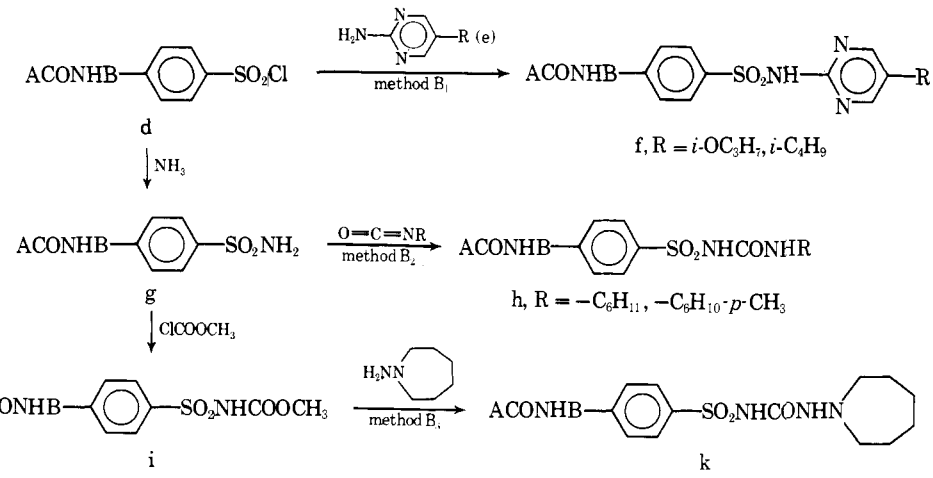
Method B. Most of the compounds were prepared following methods B. The sulfonylaminopyrimidines (f) are synthesized by reaction of a sulfonyl chloride (d) with an aminopyrimidine (e) in the presence of a suitable base like pyridine or Et_3N or with an excess of (e). The sulfonylureas (h) are prepared by reaction of the sulfonamides (g) with an appropriate isocyanate in the presence of K_2CO_3. 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 $ClSO_3H$ (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

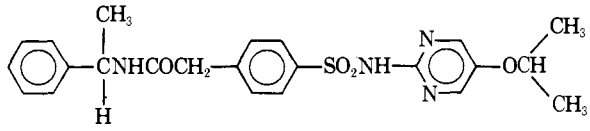
Compound **8** (Table I) is formally derived from glibenclamide (**20**), one of the most active antidiabetic drugs, by introduction of a Me substituent into the α position of the phenethylamine part (amphetamine-like structure), thus generating a chiral molecule with decreased hypoglycemic activity. 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 4231[4]). 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

method B



more active than the *S* isomer. This is in contrast to the former series of compounds[1] 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)].



22

In the preceding paper[1] 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 reported[5] 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 1-carbon 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 ±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 ±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 NH_3 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 Et_2O–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)].§

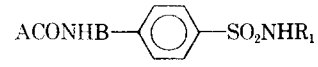
The mother liquor of the first crystallization was evaporated and the residue treated with NaOH. The liberated base was extracted with Et_2O–benzene and after evaporation treated with (−)-tartaric acid. The tartrate was collected and three times recrystallized from MeOH. Liberation of the amine and distillation afforded 28% of (*S*)-**23**: $[\alpha]^{20}D$ −33° [*c* 1 (EtOH); optical purity 96%].§

α,β-Dimethylphenethylamine (24) was prepared according to ref 10: yield 40%; bp 95–97° (12 mm).

5-Chloro-2-methoxy-*N*-(β-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 method[9] (determination of optical purity and absolute configuration by means of nmr of the diastereomeric camphor sulfonamides) is not applicable to amines of the β-alkylphenethylamine type.

Table I. Hypoglycemic Sulfonamides



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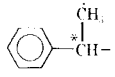
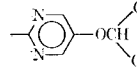
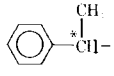
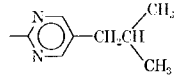
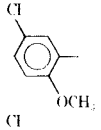
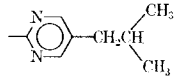
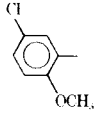
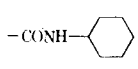
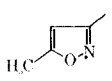
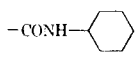
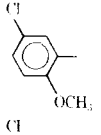
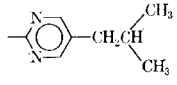
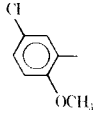
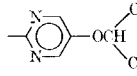
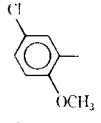
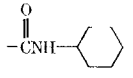
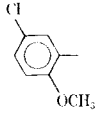
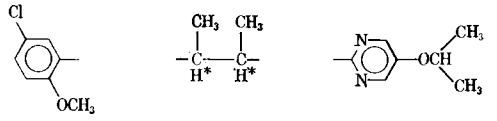
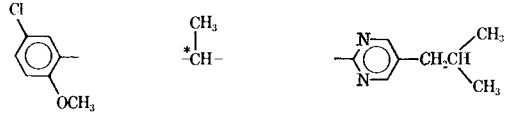
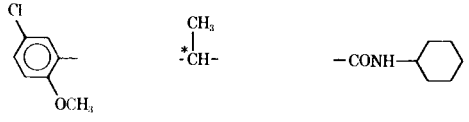
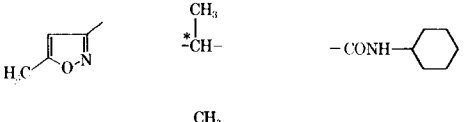
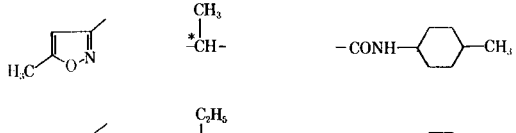
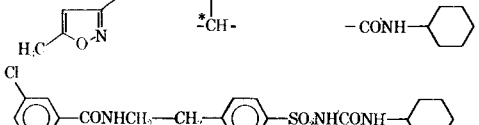
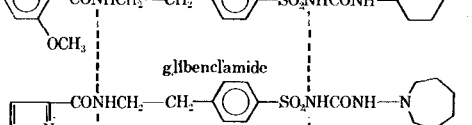
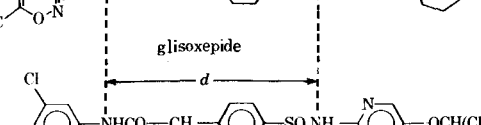
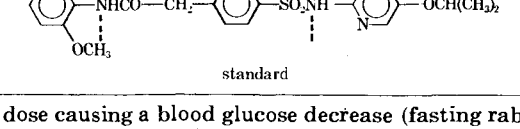
Compd	A	B	R_1	Formula	Confign at C*	$[\alpha]^{20}D$, deg	Method	Yield,[d] %	Crystn solvent	Mp,[e] °C	Dose,[a] mg/kg
5		$-CH_2CH_2-$		$C_{24}H_{28}N_4O_4S$	*R,S* *R* *S*	 +4.2 −4.1 (*c* 1, $CHCl_3$)	A A A	38 54 48	MeOH MeOH–H_2O	126 126 126	30 3[b] 30[b]
6		$-CH_2CH_2-$		$C_{25}H_{30}N_4O_3S$	*R,S*		A	32	MeOH–H_2O	136	30
7				$C_{25}H_{29}ClN_4O_4S$	*R* *S*	+24 −23 (*c* 0.5, EtOH	B_1 B_1	27 28	MeOH MeOH	138 138	3 3
8				$C_{24}H_{30}ClN_3O_5S$	*R* *S*	−4.0 +4.6 (*c* 0.5, DMF	B_2 B_2	53 33	MeOH MeOH	200 200	3 3
9				$C_{22}H_{30}N_4O_5S$	*R,S*		*i*				30
10				$C_{25}H_{29}ClN_4O_4S$	*R,S* *R* *S*	 +55.2 −55.0 (*c* 1, EtOH)	B_1 B_1 B_1	40 44 25	EtOAc MeOH MeOH	178 163 162	0.25 0.5 <1
11				$C_{24}H_{27}ClN_4O_5S$[c]	*R* *S*	+50.2 −50.2 (*c* 0.5, EtOH)	B_1 B_1	15 13	MeOH MeOH	133 133	0.5 0.25
12				$C_{24}H_{30}ClN_3O_5S \cdot H_2O$[f]	*R,S* *R* S	 +55.5 −54.7 (*c* 1, EtOH)	B_2 B_2 B_2	53 69 46	*i*-PrOH MeOH MeOH	156 157, 265[h] 264	3[b] 3[b] 3[b]
13				$C_{24}H_{31}ClN_4O_5S$	*R,S*		B_3	28	MeCN	166	1[b]

14		$C_{25}H_{29}ClN_4O_5S$[a]	*R,S*; *R,S*		B_1	40	EtOH–pet. ether	143	30
15		$C_{24}H_{27}ClN_4O_4S$	*R*	−23.4	B_1	5	*i*-PrOH–cyclohexane	110	1
			S	+23.2 (*c* 0.5, $CHCl_3$)	B_1	4	*i*-PrOH–cyclohexane	110	1
16		$C_{23}H_{28}ClN_3O_5S$	*R*	+1.4	B_2	44	MeOH	183	30
			S	−1.5 (*c* 1, MeOH)	B_2	61	EtOH	182	30
17		$C_{20}H_{26}N_4O_5S$	*R,S*		B_2[i]	75	EtOH	176	0.5
			R	+32.4	B_2	44	EtOH	192	0.25
			S	−32.0 (*c* 1, MeOH)	B_2	82	EtOH	193	30
18		$C_{21}H_{28}N_4O_5S$	*R,S*		*i*			192	0.25
			R	+34.0	B_2	74	EtOH	220	0.1
			S	−33.5 (*c* 0.5, MeOH)	B_2	70	EtOH	220	30
19		$C_{21}H_{28}N_4O_5S$	*R,S*		*i*			194	30
20		$C_{23}H_{28}ClN_3O_5S$			*j*				0.25[b]
21		$C_{20}H_{28}N_5O_5S$			*k*				0.5[b]
22		$C_{22}H_{23}ClN_4O_5S$			*l*				1

[a]Lowest dose causing a blood glucose decrease (fasting rabbits, po) which is not significantly different from that effected by 1 mg/kg of standard **22**. The dose gradation was 30, 3, 1, 0.5, 0.25, 0.1, and 0.05 mg/kg. Unless otherwise stated the compounds were applied in aqueous solution (sodium salt). For details see the Experimental Section. [b]Administered in microsuspension. [c]Uncorrected. [d]None of the reactions were run to optimum yield. [e](*R*)-**11**: *Anal.* C, H, Cl, N; S: calcd, 6.18; found, 7.04. (*S*)-**11**: *Anal.* N; S: found, 6.95. [f](*R,S*)-**12**: *Anal.* H, Cl, N, S; C: calcd, 54.8; found, 53.7. (*R*)-**12**: *Anal.* C, H, Cl, N, S. (*S*)-**12**: *Anal.* C, H, Cl, N; S: calcd, 6.08; found, 6.69. [g]**14**: *Anal.* C: calcd, 56.34; found, 55.75. H: calcd, 5.48; found, 5.83. Cl: calcd, 6.85; found, 7.44. N: calcd, 10.53; found, 9.84. S: calcd, 6.02; found, 6.88. (Nmr, ir, and uv are in agreement with the structure.) [h]Two different modifications; the nmr spectra are identical. [i]Farbenfabriken Bayer AG, Netherlands Patent 68.15633. This compound was kindly supplied by H. Horstmann and H. Plümpe, Farbenfabriken Bayer. [j]Farbwerke Hoechst AG, South African Patent 66/3675. [k]See ref 4. [l]See ref 2.

to a stirred solution of 14.9 g (0.11 mol) of 23 in 120 ml of absolute $CHCl_3$. 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 CCl_4, washed with water, dried over $MgSO_4$, and concentrated to yield 13.9 g of (*R,S*)-**25**: 83%; mp 87° (cyclohexane).‡ *Anal.* ($C_{17}H_{18}ClNO_2$) C, H, Cl, N. (*R*)-**25** gave a yield of 77%; mp 109° (CCl_4); $[\alpha]^{20}D$ +43.3° (*c* 1, EtOH). *Anal.* C, H, Cl, N. (*S*)-**25** gave a yield of 65%; mp 109° (CCl_4); $[\alpha]^{20}D$ −44° (*c* 1, 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° (CCl_4); $[\alpha]^{20}D$ −35.0° (*c* 1, EtOH). *Anal.* ($C_{17}H_{18}ClNO_2$) C, Cl, N; H: calcd, 6.0; found, 6.5. (*S*)-**26** gave a yield of 79%; mp 119° (CCl_4); $[\alpha]^{20}D$ +34.8° (*c* 1, EtOH). *Anal.* ($C_{17}H_{18}ClNO_2$) C, H, Cl, N.

5-Chloro-2-methoxy-*N*-(α-methylbenzyl)benzamide (27). (*R*)-**27** gave a yield of 94%; mp 95° (CCl_4); $[\alpha]^{20}D$ +18.0° (*c* 1, $CHCl_3$). *Anal.* ($C_{16}H_{16}ClNO_2$) C, H, Cl, N. (*S*)-**27** gave a yield of 75%; mp 94° (CCl_4); $[\alpha]^{20}D$ −17.5° (*c* 1, $CHCl_3$).

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 $CHCl_3$. 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 $CHCl_3$. The combined organic phase was dried over $MgSO_4$ 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, $CHCl_3$). (*S*)-**28** gave a yield of 90%; mp 110°; $[\alpha]^{20}D$ −80.4° (*c* 1, $CHCl_3$).

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% NH_4OH and the mixture was stirred at room temperature for 5 hr. Subsequently the mixture was diluted with 100 ml of H_2O 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°; $[\alpha]^{20}D$ +71.5° (*c* 0.25, EtOH). (*S*)-**30** gave a yield of 73%; mp 155°; $[\alpha]^{20}D$ −72.1° (*c* 0.25, EtOH). *Anal.* ($C_{17}H_{19}ClN_2O_4S$) 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); $[\alpha]^{20}D$ +35° (*c* 0.5, EtOH). (*S*)-**31** gave a yield of 87.5%; mp 133° (MeOH); $[\alpha]^{20}D$ −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)benzamide (32). (*R*)-**32** gave a yield of 25%; mp 181° (EtOH); $[\alpha]^{20}D$ +3.7° (*c* 1, MeOH). *Anal.* ($C_{16}H_{17}ClN_2O_4S$) C, H, Cl, N, S. (*S*)-**32** gave a yield of 32%; mp 180° (EtOH); $[\alpha]^{20}D$ −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°; $[\alpha]^{20}D$ +19.8° (*c* 2, MeOH). (*S*)-**33** gave a yield of 80%; mp 195°; $[\alpha]^{20}D$ −20.0° (*c* 2, MeOH). *Anal.* ($C_{13}H_{15}N_3O_4S$) N, S.

Sulfonamides of Table I (5–19). General Procedures. Method A. ***N*-[4-(5-Isopropoxy-2-pyrimidinylsulfamoyl)phenethyl]-2-phenylpropionamide (5).** Hydratropoyl chloride [prepared from 1.5 g (10 mmol) of hydratropic acid and $SOCl_2$ in absolute $CHCl_3$] dissolved in 20 ml of $CHCl_3$ was added to 3.36 g (10 mmol) of 4-(2-aminoethyl)-*N*-(5-isopropoxy-2-pyrimidinyl)benzenesulfonamide[3] in 200 ml of $CHCl_3$ and 2 ml of Et_3N. 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 B$_1$. 5-Chloro-2-methoxy-*N*-[4-(5-isobutyl-2-pyrimidinylsulfamoyl)-β-methylphenethyl]benzamide (10). (*R,S*)-**28** (3 g, 7.5 mmol) was added with stirring to 1.3 g (8.3 mmol) of 2-amino-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 $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$ and concentrated. The residue was recrystallized twice from MeOH to yield **10**: 1.7 g (44%); mp 177°.

Method B$_2$. 5-Chloro-*N*-[4-(3-cyclohexylureidosulfonyl)-β-methylphenethyl]-2-methoxybenzamide (12). Powdered K_2CO_3 (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 Me_2CO 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 Me_2CO, 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 B$_3$. 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 Me_2CO 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 Me_2CO, 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.* ($C_{20}H_{23}ClN_2O_6S$) 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 $CHCl_3$ and washed first with 100 ml of water containing 1 ml of 35% HCl and subsequently with 50 ml of water. The $CHCl_3$ layer was separated and dried over $MgSO_4$. 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 method[13] 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 test[14] ($p \leq 0.05$).

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References

(1) C. Rufer, H. Biere, H. Ahrens, O. Loge, and E. Schröder, *J. Med. Chem.*, 17, 708 (1974).
(2) E. Schröder, K. Gutsche, C. Rufer, and O. Loge, *Arzneim.-Forsch.*, in press.
(3) Boehringer, Mannheim GmbH., DOS 1770731.
(4) Farbenfabriken Bayer AG, Belgium Patent 724395.
(5) (a) H. Weber, *et al.*, *Arzneim.-Forsch.*, 19, 1326 (1969); (b) R. Heerdt, *et al.*, *ibid.*, 1346 (1969); (c) W. Aumüller, *et al.*,

‡ 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]

ibid., 1350 (1969); (d) ibid., 19 (8a), HB 419 (1969).
(6) W. A. Hartung, et al., J. Amer. Chem. Soc., 53, 1875 (1931).
(7) W. R. Brode and M. S. Raasch, J. Amer. Chem. Soc., 64, 1449 (1942).
(8) Y. Sugi and S. Mitsui, Bull. Chem. Soc. Jap., 43, 564 (1970).
(9) G.-A. Hoyer, D. Rosenberg, C. Rufer, and A. Seeger, Tetrahedron Lett., 985 (1972).
(10) A. McCoubrey and D. W. Mathieson, J. Chem. Soc., 696 (1949).
(11) E. Miller, et al., J. Amer. Chem. Soc., 62, 2101 (1940).
(12) K. Petterson, Ark. Kemi, 10, 283 (1956).
(13) A. Huggett and D. A. Nixon, Lancet, 368 (1957).
(14) E. Weber, "Grundriss der biologischen Statistik," Gustav Fischer Verlag, Stuttgart, 1967.

Hypolipidemic Substituted 1,3-Benzodioxole-2-carboxylates

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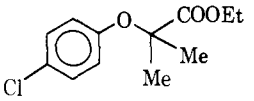
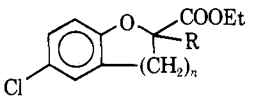
Ethyl 5-(4-fluoro-α,α-dimethylbenzyl)-1,3-benzodioxole-2-carboxylate (11, RMI 14,676) was found to be a potent hypolipidemic agent, while ethyl 5-(1-phenyl-1-cyclopentyl)-1,3-benzodioxole-2-carboxylate (19, RMI 14,654), although less potent, was found to show only minimal hepatomegaly in young rats. 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.

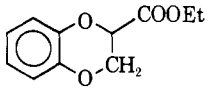
A number of investigations have been concerned with synthesizing and evaluating cyclic analogs of the hypolipidemic agent clofibrate [ethyl 2-methyl-2-(4-chlorophenoxy)propionate, I]. Thus, Witiak and coworkers[1-4] synthesized ethyl 6-chlorochroman-2-carboxylates II and III, 5-chloro-2,3-dihydro-2-benzofurancarboxylate IV, and 1,4-benzodioxane-2-carboxylate V. They found that II, IV, and V reduced serum cholesterol and triglycerides in Triton-induced hyperlipemic rats.[4] From our laboratories[5] 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 2,2-bis(*p*-chlorophenoxy)acetate (lifibrate, IX)[6] and methyl 2,10-dichloro-12*H*-dibenzo[*d*,*g*][1,3]dioxocin-6-carboxylate



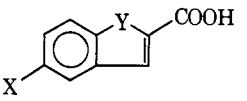
I



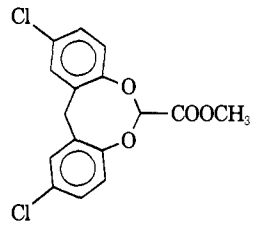
II, R = H; n = 2
III, R = CH_3; n = 2
IV, R = H; n = 1



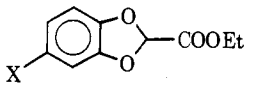
V



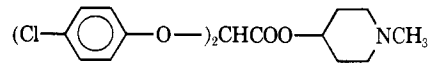
VI, Y = O, S; X = H
VII, Y = NH; X = Cl



X



VIII



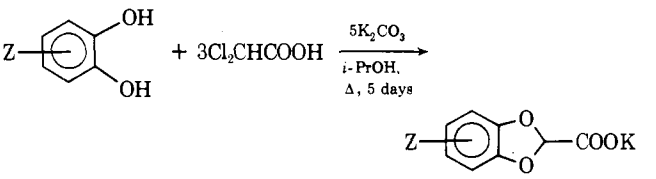
IX

(treloxinate, X)[7] the property of containing an α,α-dioxyacetate 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] Goldberg[9] 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 modification. Since 1,3-benzodioxole-2-carboxylates 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 12*H*-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-