desiccator to give 14.9 g of white solid, mp 107° dec. An aliquot was washed with ether by decantanation to give the analytical sample, mp 113° dec. *Anal.* ($C_{12}H_{17}NO_2$·HCl) C, H, N.

The following is illustrative of the preparation of the N-monosubstituted and N,N-disubstituted amidines of Table IV.

2-Ethoxy-2-phenyl-*N*-propylacetamidine Hydrochloride (94). This procedure follows that of Djerassi, *et al.*[29] In a three-necked 250-ml flask equipped with a magnetic stirrer, drying tube, and a dropping funnel was placed 7.3 g (0.030 mol) of ethyl 2-ethoxy-2-phenylacetimidate hydrochloride (L, R = Et). Absolute EtOH (40 ml) was added and the mixture stirred at ambient temperatures until complete solution occurred and then stirred in an ice bath. *n*-Propylamine previously dried over KOH (3.5 ml, 0.042 mol) was added dropwise with stirring. After the addition, the ice bath was removed and stirring was continued until the mixture warmed to room temperature and then stopped (the solution was homogeneous). After standing 43 hr the solvent was stripped below 30° on a rotary evaporator to give a yellow oily residue which was treated with 50 ml of cold 5% NaOH. This mixture was extracted with Et_2O (3 × 50 ml) and the extracts were treated with cold 1 *N* HCl (2 × 50 ml). The aqueous extract was washed once with $CHCl_3$, basified with 10% NaOH, and extracted into $CHCl_3$ (2 × 75 ml). The $CHCl_3$ extract was washed with H_2O (2 × 50 ml), dried over anhydrous K_2CO_3, charcoaled, and stripped on a rotary evaporator below 30° to give 6.7 g of yellow oil. A solution of this in 100 ml of absolute Et_2O was cooled and treated portionwise with 15 ml of 2 *N* HCl in Et_2O. The resulting suspension was cooled and the white solid collected and washed with ether to give 5.8 g (75% yield), mp 174° dec.

The following procedure was applied to the preparation of compounds **105–111.**

1-(2-Methoxy-2-phenyl-*N*-propylacetimidoyl)hexamethyleneimine (108). Methyl 2-methoxy-2-phenylacetate (10.7 g, 0.0595 mol) was converted to the *N*-propylamide by refluxing it with an excess of *n*-$PrNH_2$ overnight. The crude oil from this preparation (ir_{film} 1670 cm^{-1}) was dissolved in 100 ml of dry PhH and 12.5 g (0.06 g-atom) of PCl_5 was added all at once. The mixture was brought to reflux and boiled for 20 min at the end of which time the solid had dissolved and the solution was dark brown. The solvent and $POCl_3$ were stripped and 100 ml of PhMe was added and stripped. The stripping procedure with PhMe was repeated two more times and the residual crude imino chloride was poured with vigorous stirring into a solution of 15 ml of hexamethyleneimine and 50 ml of absolute EtOH. The mixture was kept for 2 hr at room temperature and then at reflux for 15 min. The volatile materials were removed under vacuum and the residue was taken up in 100 ml each of H_2O and Et_2O. The organic layer was extracted with two 50-ml portions of 2 *N* HCl and the combined aqueous solutions were back-washed with Et_2O. The base was liberated from the aqueous solution by the addition of 20% NaOH (ice) and was extracted into Et_2O. The dried (K_2CO_3) organic solution was concentrated and the residue was distilled under vacuum to give 5.5 g (32% yield from methyl 2-methoxy-2-phenylacetate) of a pale yellow oil: bp 116–118° (0.05 Torr); ir_{film} 1610 cm^{-1} (strong, N=C).

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Blood Glucose Lowering Sulfonamides with Asymmetric Carbon Atoms. 1

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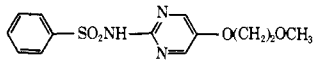
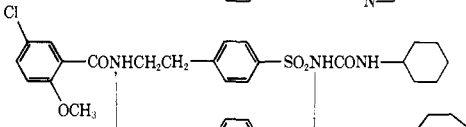
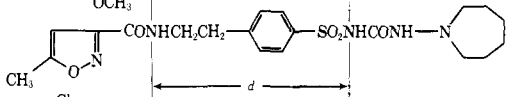
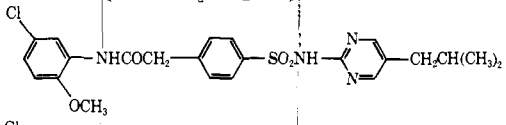
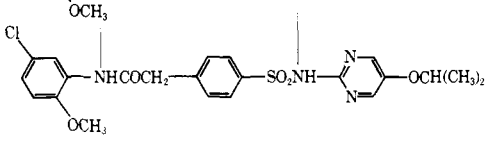
In continuation of our work on hypoglycemic sulfonylaminopyrimidines [*e.g.*, glidanile (4)] compounds with chiral carbon atoms were synthesized (compounds 18–63). The (*S*)-1-phenylethylamides of 4-[*N*-(2-pyrimidinyl)sulfamoyl]phenylacetic acid exhibit extraordinary activities, *e.g.*, compound (*S*)-46, causing blood glucose decrease at a dose of 0.05 mg/kg (rabbit). The dependency of pharmacological activity on the configuration of the asymmetric carbon atom and other structural features is discussed.

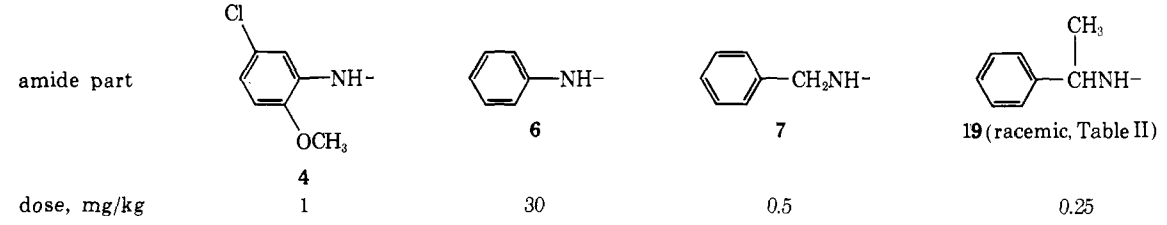
The well-known "classic" sulfonylureas, sulfonylsemicarbazides, and sulfonylaminopyrimidines [*e.g.*, glymidine (1), Table I] display blood glucose lowering activity in rabbits in a dose range of 15–30 mg/kg. In man, this corresponds to a daily dosage of 0.5–1 g. During the last few years compounds of much higher potency became known,

Table I. Some Hypoglycemic Sulfonamides Commercially Available or under Clinical Investigation (**1–4**) Compared to a Standard (**5**)

Compd (generic name)	Formula	Dose,[a] mg/kg
1 (glymidine)		30[b]
2 (glibenclamide)		0.25
3 (glisoxepide)		0.5
4 (glidanile)		1
5 (standard)		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 **5**. The dose gradation was 30; 3; 1; 0.5; 0.25; 0.1; 0.05; 0.025 mg/kg. Unless otherwise stated the compounds were applied in aqueous solution (sodium salt). For details see Experimental Section. [b] 15 mg/kg of **1** was significantly less active than 1 mg/kg of standard **5**.

Chart I



such as glibenclamide[1] (**2**), glisoxepide[2] (**3**), and glidanile[3] (**4**), respectively, being effective in the rabbit within a dose range of 0.25–1 mg/kg (Table I). This extraordinary increase in activity was achieved by substitution of the benzene nucleus with a side chain which contains a carbonamide function connected to an aromatic (carbocyclic or heterocyclic) ring system. Comparing the hypoglycemic activity of the compounds **2–5** (Table I) it is obviously of less importance whether the amide function of the side chain is built up by an aromatic acid and an aliphatic amine (ArCONH–) or vice versa (ArNHCO–). However, the distance "*d*" between the newly introduced N atom and the sulfamoyl group proves to be crucial for the activity of the compounds, and this has led to speculations concerning a second binding site of the molecule at the receptor.[3] Within a series of compounds of type **4** it has been observed[3] that the activity is dramatically reduced if the anilide nucleus is unsubstituted (**6**). However, it is increased again if a (even unsubstituted) benzylamide is present (**7**), particularly if the benzylamide is α-methyl substituted (**19**) (Chart I).

The remarkable potency of the latter substance raised the question whether or not the hypoglycemic activity of these compounds is dependent upon their stereochemistry. Though differentiation of the pharmacological potency of enantiomers is a well-known phenomenon in medicinal chemistry (*e.g.*, morphine-like analgesics, catecholamines, cholinergic agonist and antagonists[4]), nearly nothing is reported in the series of blood sugar lowering sulfonamides.†

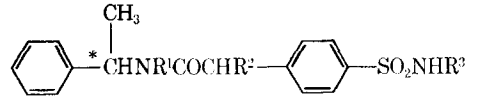
In order to study the interdependency between activity and stereochemistry and, as a result, being enabled to find better antidiabetic drugs, we synthesized a number of racemic sulfonamides and their enantiomers.

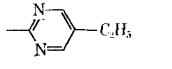
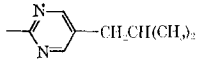
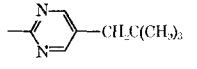
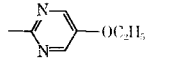
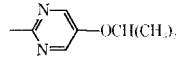
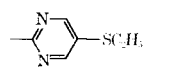
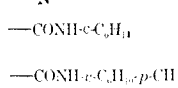
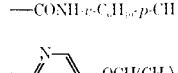
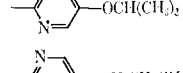
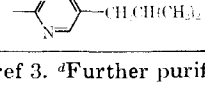
Initially we investigated the influence of the configuration of the α-methyl-substituted benzylic carbon atom on the hypoglycemic dose level in a series of compounds with different substituents in the pyrimidine or urea part of the molecule (Table II). The influence of size and kind of the residue attached to the asymmetric center can be seen in Table III, and in Table IV the distance between the asymmetric carbon atom and the carbonamide nitrogen is varied. Table V presents compounds with additional substitution of the benzene nucleus; Table VI consists of derivatives containing ring systems other than the benzene nucleus. Finally, Table VII displays the influence of an asymmetric carbon atom within the phenylacetic acid part of the molecule on the hypoglycemic activity. From the results of this investigation conclusions can be drawn about a second binding site at the receptor of the recent highly active sulfonamides.

Chemistry. Most of the sulfonamides listed in Tables II–VII have been prepared by reaction of an amine and the corresponding 4-[*N*-(2-pyrimidinyl)sulfamoyl]phenylacetyl chloride[3] as is shown below for compound (*S*)-**19**; the resulting HCl is neutralized either by an excess of amine (method A_1 in the Experimental Section) or by addition of triethylamine (method A_2). The syntheses of amines **9–14** which are not described in the literature are given in

†McMahon, *et al.*,[5] report on an optically active metabolite of 1-cyclohexyl-3-*p*-acetylphenylsulfonylurea (acetohexamide).

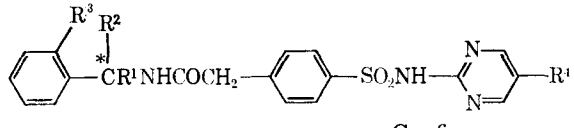
Table II. Hypoglycemic Sulfonamides



Compd	R^1	R^2	R^3	Formula[b]	Confign at *C	$[\alpha]^{20}D$, deg (c 1.0, $CHCl_3$)	Method	Yield, %	Crystn solvent	Mp, °C	Dose,[a] mg/kg
18	H	H		$C_{22}H_{24}N_4O_3S$	*R,S*[c]		A_1	47	EtOH	124	0.5
					S	−33	A_1	64	EtOH	169	0.5
					R	+35	A_2	39	EtOH	167	30
19	H	H		$C_{24}H_{28}N_4O_3S$	*R,S*[c]		A_1	64	EtOH	116	0.25
					S	−29	A_1	62	EtOH	160	0.1
					R	+29	A_1	73	EtOH	160	30
20	H	H		$C_{25}H_{30}N_4O_3S$	*S*	−26	B	50	EtOH	130	0.05
21	H	H		$C_{22}H_{24}N_4O_4S$	*R,S*[c]		A_1	91	EtOH	177	0.5
					S	−33	A_1	90	EtOH	174	0.25
					R	+32	A_2	83	EtOH	173	30
22	H	H		$C_{23}H_{26}N_4O_4S$	*R,S*[c]		A_1[d]	31	MeOH–H_2O	174	0.25
					S	−29	A_1	56	EtOH–H_2O	148	0.1
					R	+32	A_1	57	EtOH–H_2O	150	30
23	H	H		$C_{22}H_{24}N_4O_3S_2$	*S*	−44	B	16	AcOEt–C_6H_{12}	149	1
					R	+46	B[d]	20	EtOH	149	>30
24	H	H		$C_{23}H_{29}N_3O_4S$	*S*		*e*				0.25
					R	+35	C[e]	77	EtOH–H_2O	166	30
25	H	H		$C_{24}H_{31}N_3O_4S$	*S*	−62[g]	C	65	EtOH	199	0.5
					R	+60[g]	C	67	EtOH	198	30
26	H	CH_3		$C_{24}H_{28}N_4O_4S$	*S*	−15	A_1[d,f]	68	*i*-PrOH–H_2O	100	1[h]
					R	+15	A_1[d,f]	50	*i*-PrOH–H_2O	100	30[h]
27	CH_3	H		$C_{25}H_{30}N_4O_3S$	*R,S*		A_1	40	EtOH	171	30

[a] See footnote *a* in Table I. [b] N, S. [c] See ref 3. [d] Further purification by solution in dilute NaOH (in some cases, dilute NH_4OH) and precipitation with dilute HCl (in some cases, dilute AcOH). [e] See ref 7. [f] Tlc (toluene–AcOEt–AcOH, 30:60:2) shows as expected two spots (diastereomeric mixture 1:1, proved by nmr). [g] *c* 1.0, MeOH. [h] Tested as microsuspension in water.

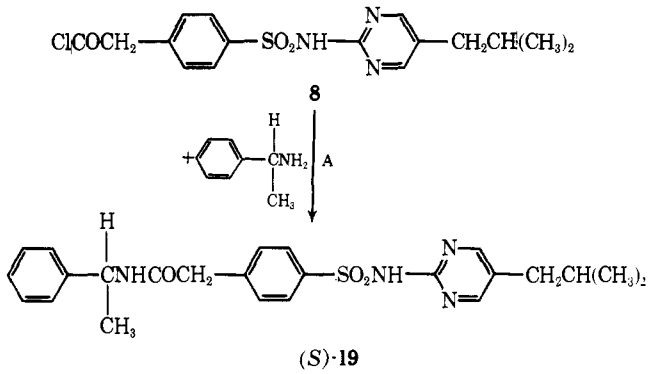
Table III. Hypoglycemic Sulfonamides



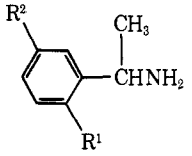
Compd	R^1	R^2	R^3	R^4	Formula[b]	Confign at *C	Method	Yield, %	Crystn solvent	Mp, °C	Dose,[a] mg/kg
28	H	C_2H_5	H	$CH_2CH(CH_3)_2$	$C_{25}H_{30}N_4O_3S$	*R,S*[c]	A_1[e]	50	EtOH	175	0.5
						S[i]	A_2[d]	10	EtOH	195	0.1
						R[i]	A_1	52	EtOH	198	>30

29	H	C_2H_5	H	$OCH(CH_3)_2$	$C_{24}H_{28}N_4O_4S$	R,S	A_1	57	$EtOH-H_2O$	175	0.25
						S[b]	A_1[c,d]	21	$MeOC_2H_4OH-H_2O$	177	0.25
						R[b]	A_1	55	EtOH	178	30
30	H	n-C_3H_7	H	$OCH(CH_3)_2$	$C_{25}H_{30}N_4O_4S$	R,S	A_1	70	EtOH	183	0.5
31	H	i-C_3H_7	H	$OCH(CH_3)_2$	$C_{25}H_{30}N_4O_4S$	R,S	A_1	58	$CHCl_3-C_6H_{12}$	193	0.5
32	H	n-C_4H_9	H	$CH_2CH(CH_3)_2$	$C_{27}H_{34}N_4O_3S$	R,S	A_1	60	$MeOC_2H_4OH-EtOH$	206	>30
33	H	n-C_4H_9	H	$OCH(CH_3)_2$	$C_{26}H_{32}N_4O_4S$	R,S	A_1	55	$MeOC_2H_4OH-EtOH$	187	30
34	H	$-CH_2CH_2-$		$CH_2CH(CH_3)_2$	$C_{25}H_{28}N_4O_3S$	R,S	A_2[e]	62	EtOH	155	30
35	H	$-CH_2CH_2CH_2-$		$CH_2CH(CH_3)_2$	$C_{26}H_{30}N_4O_3S$	R,S	A_2[e]	47	EtOH	174	3
36	H	CF_3	H	$CH_2CH(CH_3)_2$	$C_{24}H_{25}F_3N_4O_3S$	R,S	A_2[f]	28	MeCN	168	>3
37	H	$COOCH_3$	H	$CH_2CH(CH_3)_2$	$C_{25}H_{28}N_4O_5S$	R,S	A_1[g]	65	MeOH	124	30
38	H	COOH	H	$CH_2CH(CH_3)_2$	$C_{24}H_{26}N_4O_5S$	R,S	D	81	MeOH	192	>30
39	CH_3	CH_3	H	$CH_2CH(CH_3)_2$	$C_{25}H_{30}N_4O_3S$		A_1	41	$MeOC_2H_4OH-EtOH$	204	3
40	CH_3	CH_3	H	$OCH(CH_3)_2$	$C_{24}H_{28}N_4O_4S$[h]		A_2	35	EtOH	186	3[i]
41	C_2H_5	CH_3	H	$OCH(CH_3)_2$	$C_{25}H_{30}N_4O_4S$	R,S	A_2	48	$MeOC_2H_4OH-EtOH$	199	3[i]

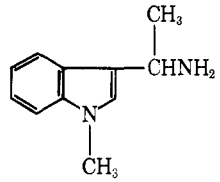
[a]See footnote *a* in Table I. [b]N, S. [c]See footnote *d* in Table II. [d]3 equiv of NEt_3 were used. [e]Only 1 equiv of (*S*)-1-phenylpropylamine was used. [f]Reaction medium: Me_2CO; after cooling of the reaction mixture the precipitate was filtered and crystallized. [g]1 equiv of 2,2,2-trifluoro-1-phenylethylammonium chloride and 3 equiv of NEt_3 were used. [h]After the end of the reaction the amine hydrochloride was filtered and the filtrate was evaporated after washing with water. [i]S: calcd, 6.84; found, 7.62. [j]$[\alpha]^{20}D$ (*c* 1.0, $CHCl_3$): (*S*)-**28**, −29°; (*R*)-**28**, +33°; (*S*)-**29**, −37°; (*R*)-**29**, +38°. [k]See footnote *h* in Table II.



the Experimental Section. The absolute configuration and the optical purity of the resolved amines used as intermediates were checked by glc and nmr of their (+)-camphorsulfonamides.[6]



9, $R^1 = OCH_3$; $R^2 = F$
10, $R^1 = OCH_3$; $R^2 = Cl$
11, $R^1 = OCH_3$; $R^2 = OCH_3$
12, $R^1 = OC_2H_5$; $R^2 = CH_3$
13, $R^1 = CH_3$; $R^2 = Cl$



14

Some of the compounds of Tables II–VII, *e.g.*, compound (*S*)-**20**, have been obtained by reaction of 5-substituted 2-pyrimidinylamines[3] with 4-chlorosulfonylphenylacetamides (method B). The 4-chlorosulfonyl compounds (*S*)- and (*R*)-**15** and **-16**, respectively, are prepared as described in the Experimental Section.

The sulfonylureas listed in Table II, *e.g.*, compound (*S*)-**25**, have been obtained from the corresponding sulfonamide and 4-methylcyclohexyl isocyanate (method C).‡ Finally, saponification of the ester **37** yielded compound **38** (Table III, method D).

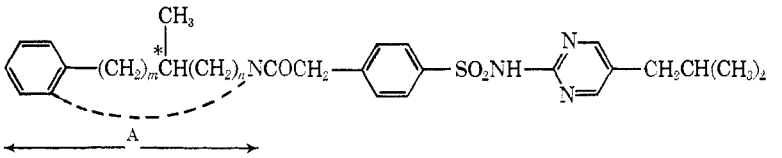
Results and Discussion

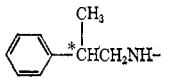
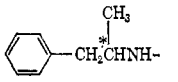
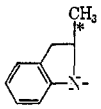
Comparison of the pharmacological data of the enantiomers of compound **19** (Table II) displayed an unexpectedly high stereospecific effect: the blood sugar lowering potency found for the *S* enantiomer (active dose, 0.1 mg/kg) is in a marked contrast to that of the *R* enantiomer (30 mg/kg). The difference in activity between the *S*- and *R*-configurated α-methylbenzylamides of 4-[*N*-(2-pyrimidinyl)sulfamoyl]phenylacetic acids was confirmed by the test results of a series of related compounds (**18–23**, Table II), the *S* form always being 30–300 times more active (rabbit) than the *R* enantiomer. This is also valid for the corresponding sulfonyl ureas **24** and **25**.‡ The stereospecific effect is not abolished by introduction of a further methyl group into the phenylacetic acid part of the molecule (this second chiral center being racemic) as it is demonstrated by compounds (*S*)- and (*R*)-**26**, respectively. However, substitution of the amide hydrogen atom by a methyl group leads to very low activity (racemic compound **27**).

The pharmacological results of the compounds of Table III allow the following conclusions about the influence of size and kind of the side chain R_2. 1. The introduction

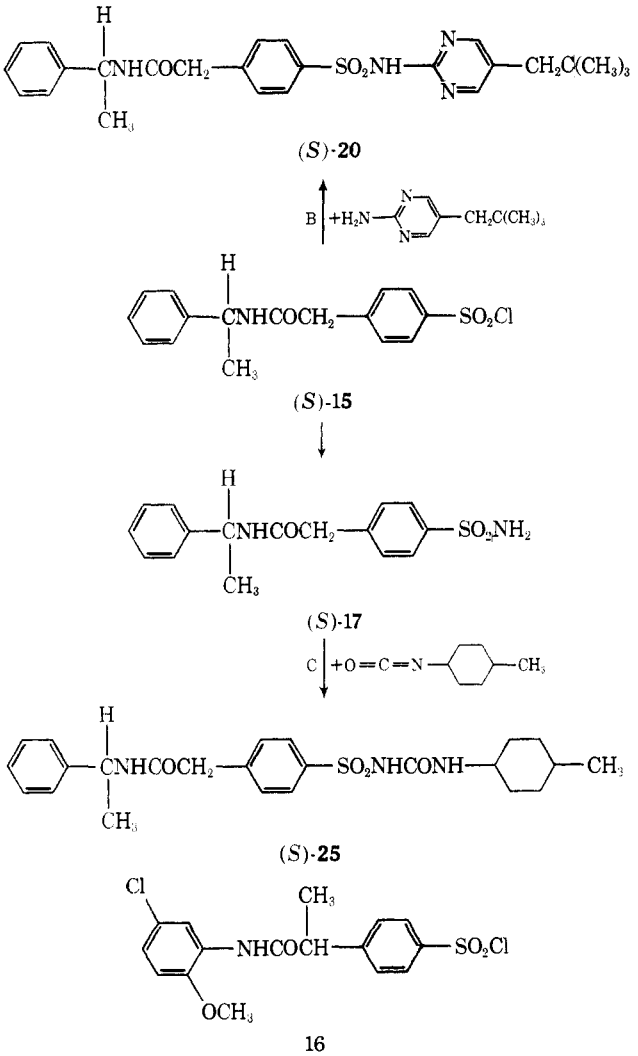
‡The authors are indebted to H. Horstmann and H. Plümpe, Farbenfabriken Bayer AG, for a supply of compound (*S*)-**24**. For the preparation of (*S*)- and (*R*)-**24** see also ref 7.

Table IV. Hypoglycemic Sulfonamides



Compd	A	Formula[b]	Config at *C	$[\alpha]^{20}D$, deg (c 1.0, EtOH)	Method	Yield, %	Crystn solvent	Mp, °C	Dose,[a] mg/kg
42		$C_{25}H_{30}N_4O_3S$	*S*	−41	A_1	28	MeOH	209	1
			R	+40	A_1	24	MeOH	208	0.5
43		$C_{25}H_{30}N_4O_3S$	*S*	−9[c]	A_1	21	MeCN	176	0.25
			R	+9[c]	A_1	22	MeCN	178	30
44		$C_{25}H_{28}N_4O_3S \cdot H_2O$	*R,S*		A_1	26	MeOH	171	>30

[a] See footnote *a* in Table I. [b] N, S. [c] *c* 0.5.



16

of an ethyl, propyl, or an isopropyl group again gives rise to highly active products (**28–31**, additionally the antipodes **28** and **29** exhibit stereospecific activity), whereas the butyl radical in **32** and **33** causes considerable loss of potency. 2. Derivatives of 1-aminoindan and 1-aminotetralin (**34** and **35**), where R_2 is bridged to the benzene nucleus, are effective only in relatively high doses. 3. The same applies to compounds **36–38**, where R_2 represents an electron-withdrawing substituent (CF_3, $COOCH_3$, or COOH). 4. Replacement of the second benzylic H atom by another alkyl group again leads to poorly active compounds (**39–41**).

The results of Table IV indicate that the stereospecific effect is lost (even though the compounds are highly active), if the chiral center is separated from the carbonamide N atom by a CH_2 group (**42**); however, it remains if the asymmetric carbon atom is not directly attached to the aromatic ring (**43**). The 2-methylindoline derivative **44** which does not possess a NH group is without any activity.

While in the anilide type certain substituents of the terminal benzene nucleus are essential for good activity;[3] they hardly influence the effective doses in the series of α-methylbenzylamides (Table V). However, the 2-methoxy (**45**) and 5-fluoro-2-methoxy compounds (**46–48**) are of special interest since they exhibit hypoglycemic activity in doses as low as 0.1 mg/kg. Therefore, the antipodes of **46** have been studied. In contrast to (*R*)-**46** which is active at about 1 mg/kg, (*S*)-**46** is one of the most potent compounds of the whole series (effective dose, 0.05 mg/kg) and is the subject of further investigation.§

As can be seen from Table VI, the benzene nucleus may be replaced by other aromatic or heteroaromatic ring systems without loss of activity, the naphthalene antipodes (*S*)- and (*R*)-**56** again showing stereospecific activity. The nonaromatic substance **61** is effective only in high doses.

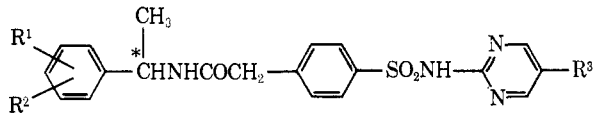
Finally, compounds **62** and **63** of Table VII have an asymmetric center in the phenylacetic acid part of the anilide type (represented by compound **7**). In contrast to the type of chiral compounds mentioned above, no differentiation of activity between (*S*)- and (*R*)-**62** is obtained. The introduction of an ethyl group (**63**) causes loss of activity.

Conclusions

The stereospecific blood glucose lowering activity of the compounds of general formula **64** with an asymmetric C atom directly attached to the N atom of the amide group gives support to the hypothesis that this N atom represents a second binding site of the molecule at the chiral

§Proposed WHO name: glioptamid.

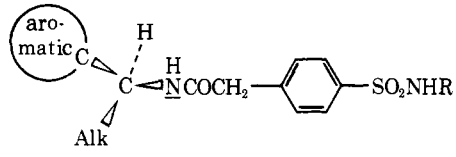
Table V. Hypoglycemic Sulfonamides



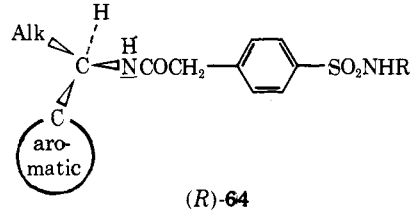
Compd	R^1	R^2	R^3	Formula[b]	Config at *C	Method	Yield, %	Crystn solvent	Mp, °C	Dose,[a] mg/kg
45	2-OCH_3	H	$CH_2CH(CH_3)_2$	$C_{25}H_{30}N_4O_4S$	*R,S*	A_2[c]	13	EtOH–*i*-PrOH	129	0.1
46	2-OCH_3	5-F	$CH_2CH(CH_3)_2$	$C_{25}H_{29}FN_4O_4S$	*R,S*	A_1	66	EtOH	134	0.1
					S[g]	A_2	58	EtOH–$CHCl_3$	162	0.05
					R[g]	A_2	74	EtOH–$CHCl_3$	164	1
47	2-OCH_3	5-F	$CH_2C(CH_3)_3$	$C_{26}H_{31}FN_4O_4S$	*R,S*	A_2[d]	24	EtOH	138	0.1
48	2-OCH_3	5-F	$OCH(CH_3)_2$	$C_{24}H_{27}FN_4O_5S$	*R,S*	A_1	44	EtOH	118	0.1
49	2-OCH_3	5-Cl	$CH_2CH(CH_3)_2$	$C_{25}H_{29}ClN_4O_4S$[e]	*R,S*	A_1	49	EtOH	130	0.25
50	2-OCH_3	5-Cl	$OCH(CH_3)_2$	$C_{24}H_{27}ClN_4O_5S$	*R,S*	A_1	50	EtOH	122	0.25
51	2-OCH_3	5-OCH_3	$CH_2CH(CH_3)_2$	$C_{26}H_{32}N_4O_5S$	*R,S*	A_1	85	EtOH–$MeOC_2H_4OH$	192	0.25
52	2-OCH_3	5-OCH_3	$OCH(CH_3)_2$	$C_{25}H_{30}N_4O_6S$	*R,S*	A_1	92	EtOH–$MeOC_2H_4OH$	176	0.5
53	2-OC_2H_5	5-CH_3	$CH_2CH(CH_3)_2$	$C_{27}H_{34}N_4O_4S$[f]	*R,S*	A_1	20	MeOH	165	0.25
54	2-CH_3	5-Cl	$CH_2CH(CH_3)_2$	$C_{25}H_{29}ClN_4O_3S$	*R,S*	A_1	45	MeOH	167	1
55	4-C_3H_7	H	$CH_2CH(CH_3)_2$	$C_{27}H_{34}N_4O_3S$	*R,S*	A_1	43	MeOH	120	>3

[a] See footnote *a* in Table I. [b] N, S. [c] See footnote *d* in Table II. [d] Reaction medium, Me_2CO. [e] S: calcd, 6.19; found, 6.76. [f] S: calcd, 6.28; found, 7.60. [g] $[\alpha]^{20}D$ (c 1.0, $CHCl_3$): (*S*), −25°; (*R*) +26°.

receptor. While the *S* enantiomers obviously fit as well or better than, *e.g.*, glidanile (**4**), into the second "keyhole" of this receptor, the *R*-configurated molecules do not fit into it; accordingly, their hypoglycemic activity in general is reduced to the level of the "classic" sulfonamides, *e.g.*, glymidine[‡] (**1**). The same seems to apply for compounds (**64**) with a bulky alkyl residue that does not fit into the second receptor site.



(*S*)-**64**



(*R*)-**64**

The dependence of the blood sugar lowering potency on the configuration of the compounds mentioned before does not seem to be restricted just to one species of animals (namely rabbits) or to the oral route of application. Thus, (*S*)- and (*R*)-*N*-(1-phenylethyl)-4-[*N*-(5-isobutyl-2-pyrimidinyl)sulfamoyl)]phenylacetamide [(*S*)- and (*R*)-**19**] display similar stereospecific effects when administered to rats (po and iv), rabbits (iv), hamsters (po and iv), dogs (po), and men (po).** Therefore, different rates of resorption of the enantiomers can probably be excluded as an explanation for the observed biological differentiation. Compound (*S*)-**19** as well as its antipode (*R*)-**19** displays an extremely low toxicity in mice (LD_{50} po, >4 g/kg; iv, 400–600 mg/kg).

‡ Compounds (*R*)-**19**, (*R*)-**46**, and (*R*)-**56** are exceptions from this rule. Their unexpectedly low effective doses can be explained by the presence of traces of the highly active *S* enantiomers.

** O. Loge, W. Losert, and W. Puls, unpublished data.

In a second paper biological results of asymmetric sulfonamides with an inverted carbon–amide group, being present in glibenclamide (**2**) and glisoxepide (**3**), respectively, will be presented.[8]

Experimental Section

General. Melting points were determined in a capillary tube and are uncorrected. Analytical data of the compounds listed in the tables obtained at least for N and S were within ±0.4% of the calculated values unless otherwise stated. Analytical data of the compounds not listed in the tables are indicated by symbols of elements if they were within ±0.4% of the calculated values. 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.

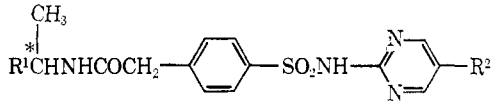
1-(5-Fluoro-2-methoxyphenyl)ethylamine (9). 5′-Fluoro-2′-methoxyacetophenone (16.8 g, 0.1 mol) was added dropwise to 25.8 g (0.4 mol) of NH_4OOCH preheated to 130°. The resulting water was distilled off at 150° (bath temperature) over 3 hr. After cooling concentrated HCl (80 ml) was added, and the mixture was refluxed for 3 hr and cooled again. After washing with PhH the aqueous phase was made alkaline with concentrated NaOH and the amine was steam distilled. NaOH (10 *N*, 15 ml) was added to the distillate and the amine was extracted with PhH. After evaporation of the solvent the amine was distilled at 110° (13 mm) to yield 9.5 g (56%). *Anal.* ($C_9H_{12}FNO$). The hydrochloride had mp 192° (*i*-PrOH–Et_2O). *Anal.* ($C_9H_{13}ClFNO$) Cl, F, N.

(*S*)- and (*R*)-1-(5-Fluoro-2-methoxyphenyl)ethylamine [(*S*)- and (*R*)-9]. A mixture of racemic **9** (16.9 g, 0.1 mol) and D(−)-tartaric acid (7.5 g, 0.05 mol) in EtOH (105 ml) was refluxed until all the material was dissolved. After standing for 24 hr at 20° the tartrate was filtered off and crystallized five times from EtOH. The amine (*S*)-**9** was liberated from the salt in the usual manner and distilled to yield 2.15 g (18%): $[\alpha]^{20}D$ −42.4° (*d* 1.12); bp 110° (13 mm). Analogously, (*R*)-**9** was obtained with L(+)-tartaric acid: $[\alpha]^{20}D$ +42.6° (*d* 1.12); bp 110° (13 mm). If a ratio of 1 mol of tartaric acid to 1 mol of racemic **9** was used for the diastereomer formation, the resolution obtained was very unsatisfactory.[6]

1-(5-Chloro-2-methoxyphenyl)ethylamine (10). Preparation analogous to **9** from 5′-chloro-2′-methoxyacetophenone gave a yield of 57%, bp 143° (18 mm). *Anal.* ($C_9H_{12}ClNO$). The hydrochloride had mp 180° (*i*-PrOH–Et_2O). *Anal.* ($C_9H_{13}Cl_2NO$) Cl, N.

1-(2,5-Dimethoxyphenyl)ethylamine (11). This was prepared analogously to **9** from 2′,5′-dimethoxyacetophenone; however, the amine was not steam distilled but extracted directly from the alkaline aqueous phase with PhH: yield 27%; bp 148° (13 mm). *Anal.* ($C_{10}H_{15}NO_2$). The hydrochloride had mp 127° (MeOH–Et_2O). *Anal.* ($C_{10}H_{16}ClNO_2$) Cl, N.

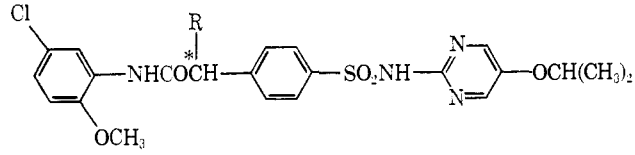
Table VI. Hypoglycemic Sulfonamides



Compd	R^1	R^2	Formula[b]	Config at *C	$[\alpha]^{20}D$, deg (c 1.0, $CHCl_3$)	Method	Yield, %	Crystn solvent	Mp, °C	Dose,[a] mg/kg
56		$CH_2CH(CH_3)_2$	$C_{28}H_{30}N_4O_3S$	*S*	−24	A_2[c,d]	24	Me_2CO–H_2O	173	0.1
				R	+27	A_2[c,d]	37	Me_2CO–H_2O	172	3
57		$CH_2C(CH_3)_3$	$C_{29}H_{32}N_4O_3S$[e]	*S*	−25	A_2	46	*i*-PrOH–Me_2CO–H_2O	167	0.25
58		$OCH(CH_3)_2$	$C_{27}H_{28}N_4O_4S$	*S*	−19	A_2	41	EtOH	185	0.25
59		$CH_2CH(CH_3)_2$	$C_{23}H_{27}N_5O_3S$	*R,S*		A_2[f]	13	EtOH–H_2O	86	0.25
60		$CH_2C(CH_3)_3$	$C_{25}H_{33}N_5O_3S \cdot H_2O$	*R,S*		A_1	44	MeCN	131	1
61		$CH_2CH(CH_3)_2$	$C_{24}H_{34}N_4O_3S$	*R,S*		A_2[d,g]	31	EtOH–H_2O	186	30

[a]See footnote *a* in Table I. [b]N, S. [c]Reaction medium, Me_2CO; after cooling, the product was filtered and crystallized. [d]See footnote *d* in Table II. [e]S: calcd, 6.19; found, 6.89. [f]Reaction medium, Me_2CO; after evaporation dilute HCl was added (pH 6) and the mixture extracted with $CHCl_3$; the evaporated extract was treated with $NaHCO_3$ solution, the filtrate acidified (pH 6), and the precipitate dissolved in dilute NH_4OH and again precipitated with dilute AcOH (pH 6). [g]A solution of 0.1 mol of acid chloride, 0.1 mol of 1-cyclohexylethylammonium chloride, and 0.16 mol of NEt_3 in Me_2CO was refluxed for 2 hr; after cooling the precipitate has dissolved in dilute NaOH and precipitated with dilute HCl.

Table VII. Hypoglycemic Sulfonamides



Compd	R	Formula[b]	Config at *C	$[\alpha]^{20}C$, deg (c 1.0, $CHCl_3$)	Method	Yield, %	Crystn solvent	Mp, °C	Dose,[a] mg/kg
62	CH_3	$C_{23}H_{25}ClN_4O_5S$	*R,S*[c]		A_1	65	EtOH–H_2O	181	3
			S	+35	B[d]	22	EtOH	167	3[e]
			R	−34	B	24	EtOH	167	3[e]
63	C_2H_5	$C_{24}H_{27}ClN_4O_5S$	*R,S*[c]		A_1	37	$MeOC_2H_4OH$–H_2O	196	>30[e]

[a]See footnote *a* in Table I. [b]N, S. [c]See ref 3. [d]Reaction solution was poured into ice–water–HCl and the product filtered off. [e]See footnote *h* in Table I.

1-(2-Ethoxy-5-methylphenyl)ethylamine (12). A mixture of 2′-ethoxy-5′-methylacetophenone (17.8 g, 0.1 mol) and $HCONH_2$ (22.5 g, 0.5 mol) was stirred at 190° for 6 hr and after cooling was poured into water. The *N*-formyl derivative of 12 was extracted with Et_2O and isolated by evaporation of the solvent. The precipitate (8.5 g, mp 103°) was refluxed with 2 *N* NaOH (200 ml) for 2.5 hr. After cooling, the amine was extracted with Et_2O. Evaporation of the solvent yielded 6.8 g (37%). *Anal.* ($C_{11}H_{17}NO$). The hydrochloride had mp 151° (EtOH). *Anal.* ($C_{11}H_{18}ClNO$) Cl, N.

1-(5-Chloro-2-methylphenyl)ethylamine (13). A solution of 5-chloro-2-methylbenzonitrile (15.2 g, 0.1 mol) in 60 ml of Et_2O was dropped into a Grignard solution generated from Mg (4.8 g, 0.2 mol) and MeI (28.4 g, 0.2 mol) in 100 ml of Et_2O. After refluxing for 10 hr the solution was chilled in an ice bath, 7.6 g of $LiAlH_4$ (0.2 mol) was added in small portions, and then the mixture was refluxed for 3 hr. After cooling 100 ml of 2 *N* NaOH was cautiously added and the inorganic solids were removed by filtration. The organic layer of the filtrate was separated and the aqueous layer as well as the inorganic precipitate was washed with Et_2O. The combined organic solution was extracted with 2 *N* HCl, then the aqueous layer basified, and the amine extracted with Et_2O. Evaporation of the solvent and distillation at 90° (1 mm) yielded 12.6 g (74%). *Anal.* ($C_9H_{12}ClN$) Cl, N. The picrate had mp 233° (EtOH).

1-(1-Methyl-3-indolyl)ethylamine (14). A mixture of 3-acetyl-1-methylindole (17.4 g, 0.1 mol), $NH_2OH \cdot HCl$ (8.3 g, 0.11 mol), K_2CO_3 (18 g, 0.13 mol), and 500 ml of EtOH was refluxed for 5 hr. After cooling the precipitate was isolated, washed with water, and treated with EtOAc. Filtration from insoluble products and evaporation of the solvent yielded 12.5 g of oxime (mp 141°), which was hydrogenated in 270 ml of EtOH on 5 g of Pd/C (10%) at 20° for 3 hr, subsequently at 40° for 4 hr. After filtration and evaporation the amine was distilled at 105° (0.01 mm) to yield 2.17 g (13%). *Anal.* ($C_{11}H_{14}N_2$).

(*S*)- and (*R*)-*N*-(1-Phenylethyl)-4-chlorosulfonylphenylacetamide [(*S*)- and (*R*)-15]. 4-Nitrophenylacetyl chloride (22 g, 0.1 mol) was added portionwise to a solution of (*S*)-1-phenylethylamine (24 g, 0.2 mol) in 70 ml of $CHCl_3$. After stirring for 16 hr at

20° the precipitate was sucked off, washed thoroughly with warm water, and dried: yield 18 g (64%) of (*S*)-*N*-(1-phenylethyl)-4-nitrophenylacetamide; mp 145°; $[\alpha]^{20}D$ −105° (c 1.0, MeOH). The *R* isomer from (*R*)-1-phenylethylamine had mp 143°; $[\alpha]^{20}D$ +103° (c 1.0, MeOH). *Anal.* ($C_{16}H_{16}N_2O_3$) C, H.

Compound **15** (28 g, 0.1 mol) in 250 ml of dioxane was catalytically hydrogenated (2.3 g of Raney Ni, 50 atm, 70°) to give after filtration, evaporation, and crystallization from EtOH 18 g (73%) of (*S*)-*N'*-(1-phenylethyl)-4-aminophenylacetamide: mp 141°; $[\alpha]^{20}D$ −71° (c 1.0, MeOH). The *R* isomer had mp 141°; $[\alpha]^{20}D$ +70° (c 1.0, MeOH). *Anal.* ($C_{16}H_{18}N_2O$) C, H.

A solution of 25 g (0.1 mol) of the 4-amino product in AcOH (160 ml) and concentrated HCl (25 ml) was treated with $NaNO_2$ (8.5 g, 0.11 mol) at about 5°. The diazonium salt solution was dropped into a mixture prepared by a solution of SO_2 (14 g) in AcOH (140 ml) and addition of $CuCl_2$ (7 g), water (14 ml), and PhH (140 ml). The mixture was stirred for 5 hr at 30° and afterwards poured onto ice; the precipitate was removed and treated with EtOAc. Filtration from insoluble products and evaporation of the solvent yielded 30 g of (*S*)-**15** (87%): mp 104°; $[\alpha]^{20}D$ −87° (c 1.0, MeOH). (*R*)-**15** had mp 105°; $[\alpha]^{20}D$ +87° (c 1.0, MeOH). *Anal.* ($C_{16}H_{16}ClNO_3S$).

(*S*)- and (*R*)-5'-Chloro-2-(4-chlorosulfonylphenyl)-2'-methoxypropionanilide [(*S*)- **and** (*R*)-**16**]. A solution of (*S*)-2-phenylpropionyl chloride [prepared from 15 g (0.1 mol) of acid, $[\alpha]^{20}D$ +81° (c 1.0, MeOH)] in 100 ml of $CHCl_3$ was added to a solution of 5-chloro-2-methoxyaniline (31.5 g, 0.2 mol) in 200 ml of $CHCl_3$ at 5–10°. After stirring for 3 hr at 30° the solution was washed with dilute HCl, then the solvent was removed, and the residue was crystallized from PhH–petroleum ether to yield 21 g (72%) of (*S*)-5'-chloro-2'-methoxy-2-phenyl propionanilide: mp 115°; $[\alpha]^{20}D$ +70° (c 1.0, $CHCl_3$). The *R* isomer from (*R*)-2-phenylpropionic acid had mp 112°; $[\alpha]^{20}D$ −71° (*c* 1.0, $CHCl_3$). *Anal.* ($C_{16}H_{16}ClNO_2$).

Chlorosulfonic acid (81 ml) was added to a solution of 29 g (0.1 mol) of the above anilide in $CHCl_3$ (140 ml) at 30°. After stirring for 16 hr at 20° the mixture was poured onto ice. The sulfonyl chloride (37 g, 95%) was obtained by extraction with $CHCl_3$ and was pure enough for the synthesis of (*S*)- and (*R*)-**62**, respectively. *Anal.* ($C_{16}H_{15}Cl_2NO_4S$).

(*S*)- and (*R*)-*N'*-(1-Phenylethyl)-4-sulfamoylphenylacetamide [(*S*)- **and** (*R*)-**17**]. A mixture of 34 g (0.1 ml) of (*S*)-**15** and 220 ml of 25% NH_4OH was stirred for 2 days at 20°. The precipitate was removed and dried to yield 30 g (92%): mp 187°; $[\alpha]^{20}D$ −90° (*c* 2.0, MeOH). The *R* isomer had mp 187°; $[\alpha]^{20}D$ +89° (c 2.0, MeOH). *Anal.* ($C_{16}H_{18}N_2O_3S$).

Sulfonamides of Tables II–VII (18–63). General Procedures. The following examples stand for methods A–D mentioned in Tables II–VII. For data and results see also Tables II–VII.

Method A_1. (*S*)-*N*-(1-Phenylethyl)-4-[*N*-(5-isobutyl-2-pyrimidinyl)sulfamoyl]phenylacetamide [(*S*)-**19**]. A solution of (*S*)-1-phenylethylamine (26 g, 0.22 mol) in 100 ml of $CHCl_3$ was added at 0° to a solution of 4-[*N*-(5-isobutyl-2-pyrimidinyl)sulfamoyl]-phenylacetyl chloride[3] (8, 38, g, 0.1 mol) in 300 ml of $CHCl_3$. After stirring for 1 hr at 20° the mixture was refluxed for 2 hr (the same yields are obtained by stirring the reaction mixture at 20° for 16 hr). The solvent was rigorously removed and the residue triturated with dilute HCl and recrystallized. THF, Me_2CO, and dioxane, respectively, were used as reaction solvents in the preparation of some compounds. In these cases the substances were isolated by evaporation of the solvent, solution of the residue in $CHCl_3$, and work-up as described above.

Method A_2. (*R*)-*N*-(1-Phenylethyl)-4-[*N*-(5-ethyl-2-pyrimidinyl)sulfamoyl]phenylacetamide [(*R*)-**18**]. A solution of (*R*)-1-phenylethylamine (13 g, 0.11 mol) and NEt_3 (11 g, 0.11 mol) in 100 ml of $CHCl_3$ was added at 0° to a solution of 4-[*N*-(5-ethyl-2-pyrimidinyl)sulfamoyl]phenylacetyl chloride[3] (32 g, 0.1 mol) in 300 ml of $CHCl_3$. The reaction was carried out and worked up as described under method A_1.

Method B. (*S*)-*N*-(1-Phenylethyl)-4-[*N*-[5-(2,2-dimethylpropyl)-2-pyrimidinyl]sulfamoyl]phenylacetamide [(*S*)-**20**]. (*S*)-*N*-(1-Phenylethyl)-4-chlorosulfonylphenylacetamide [(*S*)-**15**, 35.1 g, 0.105 mol] was added at 10° to a solution of 5-(2,2-dimethylpropyl)-2-pyrimidinylamine[3] (16.5 g, 0.1 mol) in 250 ml of pyridine. The mixture was kept for 1 hr at 20° and then for 2 hr at 65–80°; consequently it was worked up as described under method A_1.

Method C. (*S*)-1-(4-Methylcyclohexyl)-3-[4-(1-phenylethylcarbamoylmethyl)phenyl]sulfonylurea [(*S*)-**25**]. A mixture of (*S*)-*N'*-(1-phenylethyl)-4-sulfamoylphenylacetamide [(*S*)-**17**, 31.8 g, 0.1 mol] and K_2CO_3 (42 g, 0.3 mol) in 670 ml of Me_2CO was refluxed for 60 min. After addition of a solution containing 21 g (0.15 mol) of 4-methylcyclohexyl isocyanate in Me_2CO (170 ml) the mixture was refluxed for another 16 hr. After cooling the precipitate was isolated and treated with water. The insoluble products were removed by filtration and the urea was precipitated from the solution by dilute HCl, sucked off, and recrystallized. In the case of the ureas (*R*)-**24** and (*R*)-**25** the reaction mixture was cooled and the solvent evaporated. The residue was triturated with dilute HCl and dissolved in dilute NaOH. Precipitation with dilute HCl and recrystallization yielded the pure products.

Method D. *N*-[4-(5-Isobutyl-2-pyrimidinylsulfamoyl)phenylacetyl]-2-phenylglycine [(*S*)-**38**]. The methyl ester of *N*-[4-(5-isobutyl-2-pyrimidinylsulfamoyl)phenylacetyl]-2-phenylglycine (**37**, 5 g, 0.01 mol) was added to 50 ml of 2 *N* NaOH at 20° and the solution was stirred for 2 hr. After acidification with 2 *N* HCl the product was extracted with EtOAc and isolated by evaporation and recrystallization.

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 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 microsuspension, the control animals received suspension vehicle (myrg 53). The test compounds were applied in doses of 30, 3, 1, 0.5, 0.25, 0.1, 0.05, and 0.025 mg/kg until the blood glucose level was significantly higher than that caused by 1 mg/kg of standard **5**. In the case of compound 1 the dose gradation was 60, 30, and 15 mg/kg. 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[9] 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 ($p \leq 0.05$).[10]

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