Hypoglycemic Activity in Relation to Chemical Structure of Potential Oral Antidiabetic Substances. II. Analogs of 1-Sulfonyl-3-alkylureas[1]

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A number of compounds structurally related to carbutamide and tolbutamide have been prepared and tested for antidiabetic properties. None of them exerted any appreciable activity in rabbits after oral administration.

In Part I of this series[1] we reported the synthesis and hypoglycemic activity of a number of 1-sulfonyl-3-alkylureas, $RSO_2NHCONHR'$, *i.e.*, compounds closely related to the drug 1-*p*-aminobenzenesulfonyl-3-*n*-butylurea (I), *p*-$H_2NC_6H_4SO_2NHCONH(CH_2)_3CH_3$. In these compounds the alterations were restricted to the "end groups," R and R', of the molecule. We now wish to report on compounds in which modifications have been made mainly in the interjacent part of the molecule.

The compounds, Tables I-IV, either in form of aqueous solutions of their sodium salts or as suspensions in water containing 0.1% Tween 80 and 1% low viscosity CMC, were tested for hypoglycemic effect in rabbits by the method described.[1] None of the substances exerted any remarkable effect although three, 1-*p*-toluenesulfonylacetyl-3-*n*-butylurea (II), 1-β-(*p*-toluenesulfonamido)-ethyl-3-*n*-butylurea (III) and 1-*p*-toluenesulfonyl-3-isovalerylurea (IV) were slightly active.

p-$CH_3C_6H_4SO_2CH_2CONHCONH(CH_2)_3CH_3$ II

p-$CH_3C_6H_4SO_2NHCH_2CH_2NHCONH(CH_2)_3CH_3$ III

p-$CH_3C_6H_4SO_2NHCONHCO(CH_2)_2CH(CH_3)_2$ IV

(1) Part I, *J. Med. Pharm. Chem.*, **5**, 231 (1962).

TABLE I

1-ACYL- AND 1-AROYL-3-*n*-BUTYLUREAS, $RNHCONH(CH_2)_3CH_3$

R Acyl or aroyl group	M.p., °C.	Formula	Analyses Calcd., %			Found, %		
			C	H	N	C	H	N
Benzoyl	91–92	$C_{12}H_{16}N_2O_2$	65.4	7.32	12.7	65.1	7.53	12.6
p-Nitrobenzoyl-	150.5–153	$C_{12}H_{15}N_3O_4$	54.3	5.70	15.8	54.4	5.60	15.3
m-Nitrobenzoyl-	105–106	$C_{12}H_{15}N_3O_4$	54.3	5.70	15.8	54.5	5.64	15.7
o-Nitrobenzoyl-	138–139.5	$C_{12}H_{15}N_3O_4$	54.3	5.70	15.8	54.7	5.85	15.8
Phenylacetyl-	117.5–118.5	$C_{13}H_{18}N_2O_2$	66.6	7.74	12.0	66.4	7.64	11.9
β-Phenylpropionyl-	88.5–89.5	$C_{14}H_{20}N_2O_2$	67.7	8.12	11.3	68.1	8.12	11.2
Cinnamoyl-	132.5–133.5	$C_{14}H_{18}N_2O_2$	68.3	7.37	11.4	68.0	7.39	11.4
α-Methylcinnamoyl-	85–86	$C_{15}H_{20}N_2O_2$	69.2	7.74	10.8	69.4	7.75	10.9
β-Phenylisovaleryl-	82–83	$C_{16}H_{24}N_2O_2$	69.5	8.75	10.1	69.8	8.75	10.2
p-Carbethoxyamidobenzoyl-	186–187	$C_{15}H_{21}N_3O_4$	58.6	6.89	13.7	58.4	6.93	14.0
p-Methoxybenzoyl-	119.5–120.5	$C_{13}H_{18}N_2O_3$	62.4	7.25	11.2	62.7	7.29	11.4
β-Pyridoyl-	105–106	$C_{11}H_{15}N_3O_2$	59.7	6.83	19.0	59.8	6.98	18.7
γ-Pyridoyl-	112–113	$C_{11}H_{15}N_3O_2$	59.7	6.83	19.0	61.0	7.08	18.9
p-Chlorobenzoyl-	142.5–144	$C_{12}H_{15}ClN_2O_2$	56.6	5.94	11.0	56.5	6.25	10.9
Diphenylacetyl-	156–158	$C_{19}H_{22}N_2O_2$	73.5	7.15	9.03	72.9	6.97	9.08
α-Naphthoyl-	150–153	$C_{16}H_{18}N_2O_2$	71.1	6.71	10.4	70.8	6.54	10.4
p-Acetoxybenzoyl-	125–127	$C_{14}H_{18}N_2O_4$	60.4	6.52	10.1	60.2	6.65	10.0
3,5-Dinitrobenzoyl-	167.5–168.5	$C_{12}H_{14}N_4O_6$	46.4	4.55	18.1	45.7	4.55	17.8
Acetyl-	88–89.5	$C_7H_{14}N_2O_2$	53.1	8.92	17.7	53.4	8.86	17.7
Propionyl-	68.5–69.5	$C_{18}H_{16}N_2O_2$	55.8	9.37	16.3	56.0	9.54	16.5
n-Butyryl-	93.5–96	$C_9H_{18}N_2O_2$	58.0	9.74	15.0	58.4	9.46	15.0
n-Valeryl-	103–104	$C_{10}H_{20}N_2O_2$	60.0	10.1	14.0	60.7	10.0	13.9
p-Hydroxybenzoyl-	159–160.5	$C_{12}H_{16}N_2O_3$	61.0	6.83	11.9	61.9	6.93	11.9
2,4-Dichlorophenoxyacetyl-	96.5–97.5	$C_{13}H_{16}Cl_2N_2O_3$	48.9	5.05	8.78	48.7	5.18	9.03

TABLE I (*Continued*)

1-ACYL AND 1-AROYL-3-*n*-BUTYLUREAS, $RNHCONH(CH_2)_3CH_3$

R	M.p., °C.	Formula	Analyses: Calcd., % C	H	N	Found, % C	H	N
Acyl or aroyl group								
Benzenesulfonamidoacetyl-	158–159.5	$C_{13}H_{19}N_3O_4S$	49.8	6.11	13.4	50.2	6.30	13.0
p-Toluenesulfonylacetyl-	179–180.5	$C_{14}H_{20}N_2O_4S$	53.8	6.45	8.97	53.9	6.56	8.85
Benzenesulfonylacetyl-	149–150	$C_{13}H_{18}N_2O_4S$	52.3	6.08	9.39	52.1	6.26	9.25

TABLE II

1-SULFONYL-3-*n*-BUTYL-2-THIOUREAS, $RSO_2NHCSNH(CH_2)_3CH_3$

R	M.p., °C.	Formula	Analyses: Calcd., % C	H	N	Found, % C	H	N
p-Toluene-	97.5–98.5	$C_{12}H_{18}N_2O_2S_2$	50.3	6.34	9.78	50.2	6.48	9.52
Benzene-	120.5–121.5	$C_{11}H_{16}N_2O_2S_2$	48.5	5.92	10.3	48.7	6.06	10.1
Benzyl-	114–115	$C_{12}H_{18}N_2O_2S_2$	50.3	6.34	9.78	50.2	6.45	9.61
p-Fluorobenzene-	94–95	$C_{11}H_{15}FN_2O_2S_2$	45.5	5.21	9.65	45.6	5.23	9.22
α-Naphthalene-	142.5–143.5	$C_{15}H_{18}N_2O_2S_2$	55.9	5.63	8.69	55.8	5.82	8.47
p-Dimethylaminobenzene-	213–214	$C_{13}H_{21}N_3O_2S_2$	49.5	6.71	13.3	49.5	6.29	13.2

TABLE III

GUANIDINE AND SEMICARBAZIDE DERIVATIVES

Compound	M.p., °C.	Formula	Analyses: Calcd., % C	H	N	Found, % C	H	N
1-Sulfonyl-3-*n*-butylguanidines, $RSO_2NHC(=NH)NH(CH_2)_3CH_3$								
R = *p*-Toluene-	117.5–118.5	$C_{12}H_{19}N_3O_2S$	53.5	7.11	15.6	54.0	7.31	15.3
β-Naphthalene-	136.5–137.5	$C_{15}H_{19}N_3O_2S$	59.0	6.27	13.8	59.2	6.44	13.5
Benzene-	128–129.5	$C_{11}H_{17}N_3O_2S$	51.7	6.71	16.5	51.9	6.64	16.3
1-Sulfonyl-4-*n*-butylsemicarbazides, $RSO_2NHNHCONH(CH_2)_3CH_3$								
R = Benzene-	195.5–196	$C_{11}H_{17}N_3O_3S$	48.7	6.32	15.5	48.2	6.42	15.2
p-Toluene	170.5–171.5	$C_{12}H_{19}N_3O_3S$	50.5	6.71	14.7	50.6	6.70	14.7

TABLE III (*Continued*)

GUANIDINE AND SEMICARBAZIDE DERIVATIVES

Compound	M.p., °C.	Formula	Analyses: Calcd., % C	H	N	Found, % C	H	N
1-Sulfonyl-5,5-dimethylbiguanidines, $RSO_2NHC(=NH)NHC(=NH)N(CH_3)_2$								
R = Benzene-	193.5–195.5	$C_{10}H_{15}N_5O_2S$	44.6	5.61	26.0	44.6	5.69	25.6
p-Toluene-	172.5–173.5	$C_{11}H_{17}N_5O_2S$	46.6	6.05	24.7	47.1	6.29	24.1
1-*p*-Toluenesulfonyl-5-*n*-butylbiguanidine, p-$CH_3C_6H_4SO_2NHC(=NH)NHC(=NH)NH(CH_2)_3CH_3$	152–154	$C_{13}H_{21}N_5O_2S$	50.1	6.80	22.5	50.7	6.92	22.0

TABLE IV

FURTHER SULFONAMIDO COMPOUNDS

Compound	M.p., °C.	Formula	Analyses: Calcd., % C	H	N	Found, % C	H	N
1-*p*-Sulfamoylphenyl-3-*n*-butylurea $H_2NSO_2C_6H_4NHCONH(CH_2)_3CH_3$	192.5–193.5	$C_{11}H_{17}N_3O_3S$	48.7	6.32	15.5	48.8	6.33	15.2
1-*p*-Sulfamoylphenyl-3-*n*-butyl-2-thiourea $H_2NSO_2C_6H_4NHCSNH(CH_2)_3CH_3$	170–171 Lit.[4] 170–171							
1-*p*-Toluenesulfonyl-3-isovalerylurea $CH_3C_6H_4SO_2NHCONHCOCH_2CH(CH_3)_2$	154–155	$C_{13}H_{18}N_2O_4S$	52.3	6.08	9.39	52.6	6.32	9.21
1-[β-(*p*-Toluenesulfonamido)ethyl]-3-*n*-butylurea $CH_3C_6H_4SO_2NHCH_2CH_2NHCONH(CH_2)_3CH_3$	118–119.5	$C_{14}H_{23}N_3O_3S$	53.7	7.40	13.4	53.7	7.60	13.3
N-Isovaleryl-*p*-toluenesulfonamide $CH_3C_6H_4SO_2NHCOCH_2CH(CH_3)_2$	90.5–91.5	$C_{12}H_{17}NO_3S$	56.5	6.71	5.49	56.9	6.85	5.38
1-*p*-Methoxybenzenesulfonyl-3-*n*-butyl-*O*-methylpseudourea $CH_3OC_6H_4SO_2N=C(OCH_3)NH(CH_2)_3CH_3$	66.5–67.5	$C_{13}H_{20}N_2O_4S$	52.0	6.71	9.32	51.6	6.68	9.58

A few compounds, especially 1-β-pyridoyl-3-*n*-butylurea, 1-*p*-dimethylaminobenzenesulfonyl-3-*n*-butylthiourea and the sulfonyl derivatives of biguanidine, showed hyperglycemic activity. Similar observations with pyridoylbutylurea have been reported recently.[2] The effect of the biguanidine derivatives is rather surprising, as the parent alkylbiguanidines are well known to exert powerful hypoglycemic activity.[3]

It has been suggested[1] that in the hypoglycemic sulfonylurea derivatives, $RSO_2NHCONHR'$, the function of the groups R and R′ might be to provide the compounds with favorable physical properties whereas the interjacent part of the molecule might exert more specific chemical functions. The results discussed in the present paper stress this suggestion and illustrate that the structural requirements of this part are indeed very rigorous as even the substitution of the oxygen atom of the urea moiety by sulfur, which can hardly appreciably alter the physical properties of the compound, completely destroys the activity.

Experimental

The compounds used in this investigation all were prepared by well-known reactions. Only a few of them appear to have been described in the literature. Melting points and analytical data of the new substances are listed in Tables I-IV. The melting points are corrected.

1-Acyl- and 1-Aroyl-3-*n*-butylureas.—The appropriate acid chloride (0.2 mole) was added in portions to a mixture of *n*-butylurea (0.24 mole) and anhydrous pyridine (30 ml.). When the initial exothermic reaction had subsided the mixture was heated at 100–110° for about 2 hr., and then poured into water. The solid that formed was filtered off and crystallized from ethanol or aqueous ethanol. The yield of material once recrystallized was in the order of 50 to 85%.

Benzenesulfonylacetyl and *p*-toluenesulfonylacetyl chloride were obtained by refluxing the acids (0.4 mole) with thionyl chloride (150 ml.) and removing the excess thionyl chloride under reduced pressure on the water bath, and were used in the subsequent reaction without purification. **Benzenesulfonamidoacetyl chloride**, similarly prepared, was purified by crystallization from benzene–petroleum ether, and formed needles, m.p. 86–88°.

Anal. Calcd. for $C_8H_8ClNO_3S$: Cl, 15.2. Found: Cl, 14.9.

1-*p*-Hydroxybenzoyl-3-*n*-butylurea was obtained from its acetate ester by heating this (35 g.) in a mixture of sodium hydroxide (20 g.), ethanol (150 ml.) and water (50 ml.) for 0.5 hr. on the water bath, diluting with water (500 ml.),

(2) Th. Wagner-Jauregg, W. Taterka, and O. Büch, *Arzneimittel-Forsch.*, **10**, 686 (1960).
(3) K. H. Slotta and R. Tschesche, *Ber.*, **62**, 1398 (1929).

filtering, precipitating by acidification with dilute hydrochloric acid and crystallization from aqueous ethanol.

1-Sulfonyl-3-*n*-butyl-2-thioureas.—The sodium salt of the appropriate sulfonamide (0.2 mole), *n*-butyl isothiocyanate (0.3 mole) and freshly distilled nitrobenzene (75 ml.) were heated at 120–140° for about 15 hr. with occasional shaking. The solvent was distilled off with steam, the aqueous solution of the thiourea treated with decolorizing carbon and filtered. Acidification of the filtrate with acetic acid afforded the desired product usually as an oil which soon solidified. It was purified by crystallization from methanol. The yield of crude material was 60 to 80%.

1-Sulfonyl-3-*n*-butylguanidines.—To a stirred mixture of di-(*n*-butylguanidine) sulfate (0.1 mole), the appropriate sulfonyl chloride (0.2 mole) and acetone (200 ml.), there was added over 1 hr. a solution of sodium hydroxide (25 g.) in water (50 ml.), the temperature being kept at 20–25°. Stirring was continued for a further hr., water (500 ml.) was then added and the solid precipitate filtered off and crystallized from methanol.

1-Sulfonyl-5-*n*-butyl- and -5,5-dimethylbiguanidines were prepared similarly from the corresponding biguanidine hydrochlorides.

1-*n*-Butylbiguanidine Hydrochloride.—Cupric chloride dihydrate (341 g.) was dissolved in water (500 ml.) and added to dicyanodiamide (168 g.) and *n*-butylamine (250 g.). The mixture was refluxed for 20 hr., and after cooling the pink copper complex was filtered off, washed with dilute ammonia and water and dissolved in 4 *N* hydrochloric acid (600 ml.). The solution was saturated with hydrogen sulfide, the copper sulfide filtered off and washed with dilute hydrochloric acid, and the combined filtrate and washings were evaporated *in vacuo* on a water bath. The resulting syrup was dissolved in absolute ethanol (250 ml.) and again evaporated, this operation being repeated twice more. The anhydrous sticky mass was dissolved in absolute ethanol (150 ml.) and carefully treated with ether (250 ml.). The butylbiguanidine hydrochloride separated as faintly yellow leaflets, which were filtered off and dried; yield, 183 g. This product was purified by solution in the minimum amount of ethanol and reprecipitation with ether, yielding 173 g. of a product melting at 163–165° (dec.).

Anal. Calcd. for $C_6H_{16}ClN_5$: Cl, 18.4. Found: Cl, 18.2.

1-Sulfonyl-4-*n*-butylsemicarbazides.—These were obtained by treatment of the appropriate sulfonyl hydrazide (0.1 mole) with *n*-butyl isocyanate (0.12 mole) in dioxane (75 ml.) at 70–90° until a clear solution resulted. The product was precipitated by the addition of water and crystallized from aqueous methanol.

1-*p*-Toluenesulfonyl-3-isovalerylurea.—To a mixture of *p*-toluenesulfonylurea (42.8 g., 0.2 mole) and isovaleryl chloride (30 g., 0.25 mole) was added anhydrous pyridine (25 ml.) in small portions with shaking and cooling with tap water. When the reaction subsided the mixture was heated for 2 hr. on a water bath and then poured into water. The precipitated oil solidified on scratching, needles from methanol.

1-*p*-Sulfamoylphenyl-3-*n*-butylurea.—*n*-Butyl isocyanate (0.11 mole), sulfanilamide (0.10 mole), and dioxane (100 ml.) were refluxed for 10 hr. The clear solution was diluted carefully with water, and the solid precipitate crystallized from methanol. **1-*p*-Sulfamoylphenyl-3-*n*-butyl-2-thiourea** was analogously prepared

from *n*-butyl isothiocyanate.

1-β-(*p*-Toluenesulfonamido)-ethyl-3-*n*-butylurea.—*p*-Toluenesulfonamidoethylamine (0.15 mole) was treated with *n*-butyl isocyanate (0.18 mole) for 4 hr. on the water bath. The oily product was cooled and triturated with methanol, and the solid obtained crystallized from aqueous methanol.

***N*-*n*-Valeryl-*p*-toluenesulfonamide.**—The sodium salt of *p*-toluenesulfonamide (29 g.) was suspended in anhydrous dioxane (100 ml.). *n*-Valeryl chloride (21 g.) was added and the mixture heated on the water bath for 2 hr. and poured into water. The solid product was filtered off and crystallized from benzene and from methanol.

1-*p*-Methoxybenzenesulfonyl-3-*n*-butyl-*O*-methylpseudourea.—To a stirred solution of *N*-*n*-butyl-*O*-methylpseudourea (26 g.), and triethylamine (30 ml.) in dioxane (50 ml.) there was added dropwise a solution of *p*-methoxybenzenesulfonyl chloride (23 g.) in dioxane (100 ml.) at 5–10°. Stirring was continued for 2 hr. after completed addition, the mixture was diluted with water (500 ml.) and made alkaline with 6 *N* sodium hydroxide. The precipitated product was collected and crystallized from aqueous ethanol.

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(4) J. S. Roth and E. F. Degering, *J. Am. Chem. Soc.*, **67**, 126 (1945).