SYNTHESIS AND HYPOGLYCEMIC ACTIVITY OF 4-(β-ACYLAMIDOETHYL)BENZENESULFONAMIDES

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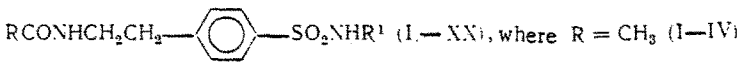
During the eighties, hypoglycemic preparations of the sulfon-amide series became important again. New concepts appeared that confirmed their mechanism of action [1], and the search for new active compounds of this class has been reviewed.

In the present work, the results are reported of the synthesis and examination of the hypoglycemic activity in the series of N-substituted benzenesulfonamides of the general formula

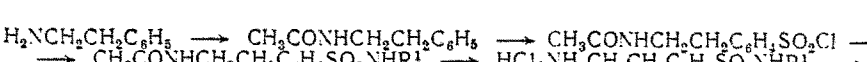


$RCONHCH_2CH_2$—C$_6$H$_4$—SO_2NHR^1 (I—XX), where R = CH_3 (I—IV),

2-CH_3O-3-ClC_6H_3 (V—XI) 3-$ClC_6H_4CH{=}CH$ (XII), 3 ClC_6H_4 (XIII),
$C_6H_5CH_2CH_2$ (XIV, XV), $C_6H_5CH{=}CCH_2$ (XVI, XVII), 3-$CH_3OC_6H_4CH{=}CH$ (XVIII),
4-$ClC_6H_4OCH_2$ (XIX, XX); R^1 = c-C_6H_{11} (I, VI, XIII, XV, XVI, XVIII, XIX),
$C_6H_5CH_2CH_2$ (II, V, XII, XIV, XVII), 5-isopropyl-1,3,4-thiadiazolyl (III, VII),
p-(5-ethyl-1,3,4-thiadiazolylsulfamido)-phenylene IV, VIII), 1,3,4-triazolyl (IX),
5-isobutyl-1,3,4-thiadiazolyl (X), 1-adamantyl (XI), $CONHC_6H_{11}$ (XX).

The required end products were synthesized by two schemes, depending on the nature of R. If R was unreactive with respect to the sulfochlorinating agents (compounds I-IV), the β-phenylethylamine was acylated by a carboxylic acid chloride, the acyl derivative was introduced into a reaction with chlorosulfonic acid, and the sulfonyl chlorides formed were condensed with amines NH_2R^1.

If R was reactive, the synthesis was complicated, since the amino group had to be preliminarily protected by an acetyl residue and then the sulfoamidation, saponification of the acetamide group, and reacylation of the β-aminoethylbenzenesulfonamides by an acid chloride RCOCl were carried out according to the following scheme:



$H_2NCH_2CH_2C_6H_5 \longrightarrow CH_3CONHCH_2CH_2C_6H_5 \longrightarrow CH_3CONHCH_2CH_2C_6H_4SO_2Cl \longrightarrow$
$\longrightarrow CH_3CONHCH_2CH_2C_6H_4SO_2NHR^1 \longrightarrow HCl{\cdot}NH_2CH_2CH_2C_6H_4SO_2NHR^1 \longrightarrow$
$\longrightarrow$ V—XX

EXPERIMENTAL CHEMICAL PART

4-(β-Acetamidoethyl)benzene-N-cyclohexylsulfonamide (I). The 52.3-g portion (0.2 mole) of 4-(β-acetamidoethyl)benzenesulfonyl chloride, synthesized by a known method [2], was added to 72 ml (0.62 mole) of cyclohexylamine. The reaction mixture was held for 4 h on a boiling water bath. It was then cooled, 900 ml of dilute (1:3) hydrochloric acid was added, and the mixture was stirred for 30 min. The precipitate was filtered, washed on the filter with distilled water, and recrystallizaed from alcohol. The yield of I was 70.4 g (75.6%), mp 131-132°C. Found, %: N 7.60; S 9.27. $C_{16}H_{28}N_2O_3S$. Calculated, %: N 7.95; S 9.09. IR spectrum, ν_{max}, cm^{-1}: 1650 (C=O); 1325 (SO_2 asymm.); 1160 (SO_2 symm.); 3368 (N-H).

4-(β-Acetamidoethyl)-benzene-N-(β-phenylethyl)sulfonamide (II) was obtained by a method similar to that for I. The yield of II was 69.9%, mp 127-128°C. Found, %: N 7.92; S 9.0. $C_{18}H_{24}N_2O_3S$. Calculated, %: N 8.04; S 9.19. IR spectrum, ν_{max}, cm^{-1}: 1650 (C=O); 1160 (SO_2); 3410 (N-H).

4-(β-Acetamidoethyl)-benzene-N-[2-(5-isopropyl)-thiadiazolyl]-sulfonamide (III). A 1.43-g portion (0.01 mole) of 2-amino-5-isopropylthiadiazole was dissolved in 20 ml of dry pyridine and 2.62 g (0.01 mole) of 4-(β-acetamidoethyl)benzenesulfonyl chloride was added. The mixture was heated on a boiling water bath for 4 h. It was then cooled and 25 ml of 10% hydrochloric acid was added. The mixture was then shaken for 5 min, allowed to settle, and the aqueous

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layer was decanted. To the residue, 20 ml of 5% HCl was added, and the mixture was stirred for 15 min. The solid product was filtered, washed on the filter with water, and recrystallized from ethanol. The yield of III was 1.87 g (50.8%), mp 150-151°C. Found, %: N 15.44; S 17.60. $C_{15}H_{20}N_4O_3S_2$. Calculated, %: N 15.21; S 17.39,

4-(β-Acetamidoethyl)-benzene-N-[4-phenylenesulfamido-5-(2-ethylthiadiazolyl)]-sulfonamide (IV) was obtained by a method similar to that for III. The yield of IV was 67.4%, mp 241-243°C. Found, %: N 13.80; S 18.70; $C_{20}H_{23}N_5O_5S_3$. Calculated, %: N 13.75; S 18.86. IR spectrum, ν_{max}, cm^{-1}: 1670 (C=O); 1305, 1345, 1147 (SO_2); 3400, 3200 (N-H).

4-[β-2-Methoxy-5-chlorobenzamido)-ethyl]benzene-N-(β-phenylethyl)sulfonamide (V). A 3.68-g portion (0.01 mole) of II was boiled for 4 h with 20 ml of 15% HCl. The mixture was then cooled and the precipitate was filered and suspended in 40 ml of dioxane. A 2-ml portion of triethylamine was added to the suspension, and, while a temperature of 10-12°C was maintained in the reaction zone, a solution of 1.93 g (0.01 mole) of 2-methoxy-5-chlorobenzoyl chloride in 10 ml of dioxane was added dropwise. The reaction mixture was boiled for 2 h, then cooled, triethylamine hydrochloride was separated by filtration, 30 ml of 5% HCl was added to the filtrate, and the mixture was stirred for 10 min. The oily layer was separated and washed thrice with ether; the residue was recrystallized from a mixture of alcohol with water (1:1). The yield of V was 2.73 g (58%), mp 126-127°C. Found, %: Cl 7.82; N 5.98; S 6.33. $C_{24}H_{25}ClN_2O_4S$. Calculated, %: Cl 7.51; N 5.92; S 6.77. IR spectrum, ν_{max}, cm^{-1}: 1650 (C=O); 1330, 1170 (SO_2); 3410 (N-H).

4-[β-(2-Methoxy-5-chlorobenzamido)-ethyl]benzene-N-cyclohexylsulfonamide (VI) was obtained by a method similar to that for V. The yield of VI was 66%, mp 219-220°C Found, %: Cl 7.96; N 5.82; S 6.84. $C_{22}H_{27}ClN_2O_4S$. Calculated, %: Cl 7.88; N 6.21; S 7.10.

4-[β-(2-Methoxy-5-chlorobenzamido)ethyl]benzene-N-[2-(5-isopropylthiadiazolyl)]sulfonamide (VII). A 3.8-g portion (0.01 mole) of 4-[β-(2-methoxy-5-chlorobenzamido)-ethyl]benzenesulfonyl chloride, obtained by known method [2], was fused with 1.5 g (0.01 mole) of 2-amino-5-isopropylthiadizaole, while the temperature in the reaction zone was gradually increased from 80 to 150°C. The cooled melt was recrystallized twice from ethanol. The yield of VII was 2.7 g (47.2%), mp 170-172°C. Found, %: Cl 7.44; N 11.35; S 13.1. $C_{21}H_{23}ClN_4O_4S_2$. Calculated, %: Cl 7.17; N 11.32; S 12.94.

4-[β-(2-Methoxy-5-chlorobenzamido)-ethyl]benzene-N-[4-phenylenesulfamido-2-(5-ethylthiadiazolyl)]sulfonamide (VIII) was obtained by a method similar to that for VII. The yield of VIII was 56.8%, mp 180-181°C. Found, %: Cl 5.31; N 11.21; S 15.48. $C_{26}H_{26}ClN_5O_6S_3$. Calculated, %: Cl 5.58; N 11.01; S 15.10.

4-[β-(2-Methoxy-5-chlorobenzamido)-ethyl]benxene-N-(1,3,4-triazoly)sulfonamide (IX) was obtained by a method similar to that for VII. The yield of IX was 34.6%, mp 156-158°C. Found, %: Cl 7.94; N 15.88; S 7.80. $C_{18}H_{17}ClN_5O_4S$. Calculated, %: Cl 8.17; N 16.11; S 7.36. IR spectrum, ν_{max}, cm^{-1}: 1630 (C=O) 1358, 1170 (SO_2), 3322 (N-H).

4-[β-(2-Methoxy-5-chlorobenzamido)-ethyl]benzene-N-[2-(5-isobutyl)thiadiazolyl]sulfonamide (X) was obtained by a method similar to that for VII. The yield of X was 71%, mp 180-182°C. Found, %: Cl 7.04; N 10.82; S 12.70. $C_{22}H_{25}ClN_4O_4S_2$. Calculated, %: Cl 6.98; N 11.01; S 12.58. IR spectrum, ν_{max}, cm^{-1}: 1640 (C=O); 1305, 1170 (SO_2); 3400 (N-H).

4-[β-(2-Methoxy-5-chlorobenzamido)-ethyl]benzene-N-(1-adamantyl)sulfonamide (XI) was obtained by a method similar to that for III. The yield of XI was 68.2%, mp 150-152°C. Found, %: Cl 7.32; N 5.42; S 6.87. $C_{26}H_{31}ClN_2O_4S$. Calculated, %: Cl 7.06; N 5.57; S 6.36. IR spectrum, ν_{max}, cm^{-1}: 1645 (C=O); 1330, 1157 (SO), 3395 (N-H).

4-{β-[2-(3-Chlorophenyl)acrylamido]ethyl}benzene-N-(β-phenylethyl)sulfonamide (XII) was obtained by a method similar to that for III. The yield of XII was 57.2%, mp 155-156°C. Found, %: Cl 7.55; N 6.34; S 6.66. $C_{25}H_{25}ClN_2O_3S$. Calculated, %: Cl 7.57; N 5.07; S 6.83.

4-{β-[2-(3-Chlorophenyl)acrylamido]ethyl}benzene-N-cyclohexylsulfonamide (XIII) was obtained by a method similar to that for III. The yield of XIII was 46%, mp 168-169°C. Found, %: Cl 8.14; N 6.22; S 7.28. $C_{23}H_{27}ClN_2O_3S$. Calculated, %: Cl 7.95; N 6.27; S 7.16.

4-[β-(2-Phenylpropionylamido)ethyl]benzene-N-(β-phenylethyl)sulfonamide (XIV) was obtained by a method similar to that for V. The yield of XIV was 41.4%, mp 111-112°C. Found, %: N 6.61; S 7.56. $C_{25}H_{28}N_2O_3S$. Calculated, %: N 6.42; S 7.33. IR spectrum, ν_{max}, cm^{-1}: 1670 (C=O); 1325, 1170 (SO_2); 3400 (N-H).

TABLE 1. Influence of 4-(β-Acylamidoethyl)benzenesulfonamides on Glycemia of Intact Rats

Compound	Dose, mg/kg	Number of animals	Change in glycemia after introduction of compounds								
			after 3 h			after 6 h			after 9 h		
			decrease, %	P_1	P_2	decrease, %	P_1	P_2	decrease, %	P_1	P_2
V	100	7	−11.9	<0.02	<0.05	−17.4	<0.01	<0.05	−26.5	<0.001	<0.001
VI	50	10	−16.1	<0.01	<0.05	−25.16	<0.001	<0.01	−30.22	<0.001	<0.001
VI	150	10	−26.8	<0.001	<0.001	−32.6	<0.001	<0.001	−38.6	<0.001	<0.001
VII	50	7	−10.1	<0.05	—	−11.2	<0.05	—	−23.0	<0.001	<0.01
VII	200	10	−19.2	<0.01	<0.05	−28.5	<0.001	<0.01	−33.0	<0.001	<0.01
IX	100	10	−12.9	<0.01	<0.05	−12.2	<0.01	<0.05	−14.2	<0.01	<0.02
XI	200	10	−9.0	<0.05	—	−20.1	<0.01	<0.05	−28.4	<0.001	<0.02
XIV	200	10	−11.7	<0.01	<0.05	−15.2	<0.001	<0.05	−23.5	<0.001	<0.05
XIX	200	7	−3.1	—	—	−15.6	<0.02	<0.05	−17.9	<0.01	<0.05
XX	20	7	−22.8	<0.01	<0.05	−30.6	<0.001	<0.001	−38.9	<0.001	<0.001

Note. P_1 — reliability of difference, compared with initial level, P_2 — compared with control.

4-[β-(2-Phenylpropionylamido)ethyl]benzene-N-cyclohexylsulfonamide (XV) was obtained by a method similar to that for III. The yield of XV was 47%, mp 137-139°C. Found, %: N 6.89; S 7.76. $C_{23}H_{30}N_2O_3S$. Calculated, %: N 6.70; S 7.72. IR spectrum, ν_{max}, cm^{-1}: 1650 (C=O); 1325, 1160 (SO_2); 3390 (N-H).

4-[β-(1-Methyl-2-phenylacrylamido)ethyl]benzene-N-cyclohexylsulfonamide (XVI) was obtained by a method similar to that for III. The yield of XVI was 30.5%, mp 160-161°C. Found, %: N 6.38; S 7.32. $C_{24}H_{30}N_2O_3S$. Calculated, %: N 6.57; S 7.51.

4-[β-(1-Methyl-2-phenylacrylamido)ethyl]benzene-N-(β-phenylethyl)sulfonamide (XVII) was obtained by a method similar to that for V. The yield of XVII was 47.8%, mp 129-130°C. Found, %: N 6.28; S 7.21. $C_{26}H_{28}N_2O_3S$. Calculated, %: N 6.25; S 7.14. IR spectrum, ν_{max}, cm^{-1}: 1650 (C=O); 1325, 1169 (SO_2).

4-[β-(3-Methoxyphenylacrylamido)ethyl]benzene-N-cyclohexylsulfonamide (XVIII) was obtained by a method similar to that for III. The yield of XVIII was 56%, mp 138-139°C. Found, %: N 6.67; S 7.35. $C_{24}H_{30}N_2O_4S$. Calculated, %: N 6.33; S 7.23.

4-[β-(4-Chlorophenoxyacetamido)ethyl]benzene-N-cyclohexylsulfonamide (XIX) was obtained by a method similar to that for III. The yield of XIX was 40%, mp 99-100°C. Found, %: Cl 7.46; N 6.70; S 7.64. $C_{22}H_{27}ClN_2O_4S$. Calculated, %: Cl 7.88; N 6.21; S 7.10.

N-4-[β-(p-Chlorophenoxyacetamido)ethyl]benzenesulfonyl-N^1-cyclohexylurea (XX). A 3.4-g portion (0.1 mole) of 4-[β-(phenoxyacetamido)ethyl]benzenesulfonamide, synthesized in analogy with the data in [3], was dissolved in 50 ml of analytically pure acetone, 2.7 g (0.02 mole) of a freshly calcined potassium carbonate were added, followed by a slow dropwise addition of an acetone solution of cyclohexyl isocyanate (1.9 g, 0.015 mole in 15 ml of acetone), and the mixture was boiled for 4 h. The reaction mixture was cooled, the precipitate was separated by filtration, 40 ml of ethanol were added, and the mixture was boiled for 5 min. It was then acidified with hydrochloric acid to pH 4.0, and the hot solution was filtered. The filtrate was allowed to stand for 24 h for crystallization. A white crystalline compound was obtained, mp 174-175°C. The yield of XX was 2.75 g (60%). Found, %: Cl 7.35; N 8.32; S 6.80. $C_{23}H_{28}N_3O_3S$. Calculated, %: Cl 7.19; N 8.51; S 6.48. The IR spectrum was run on a UR-20 spectrophotometer with LiF, NaCl prisms in KBr tablets.

EXPERIMENTAL PHARMACOLOGICAL PART

The hypoglycemic action of sulfonamides (50-200 mg/kg) was studied in intact male rats, weighing 200-250 g each. The compounds were introduced orally in the form of a suspension in 1% starch mucilage. The blood sugar level (BSL) was determined by the orthotoluidine method 3, 6, and 9 h after the administration.

Hypoglycemic activity was revealed in 9 out of 19 of the compounds syntehsized; the data on the most effective among them are given in Table 1. The pharmacological activity of the compounds tested depends on the nature of the R residue and the substituent of the sulfonamide group R^1. Acetyl derivatives containing different R^1 do not cause a statistically reliable change in the level of glycemia in intact rats. Sulfonamides containing a 2-methoxy-5-chlorobenzoyl substituent (V-XI) have different intensity of the hypoglycemic action, depend-

ing on the nature of R^1. The most effective were found to be compounds VI, VII, XV, for which R^1 = cyclohexyl, 2-(5-isopropylthiadiazolyl), and 1-adamantyl, respectively.

Compound VI is a structural analog of a second generation preparation, glybenclamide; they differ in that glybenclamide contains a sulfonylurea group, while VI contains a sulfonylamide grouping. As is known [4], glybenclamide is effective in a dose of 1 mg/kg, whereas VI causes an equivalent hypoglycemic effect only in a dose of 150 mg/kg. In a similar way, the ratio of the effective doses of compound XIX (sulfonamide) and XX (sulfonylurea) is 20/200. These facts indicate that the transition from the sulfonamide group to a sulfonylurea group increases the hypoglycemic activity of a compound by tens of times.

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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF N-ALKYLPYRIDINIUM-4-CARBOXALDEHYDE N-ACYLGLYCYL- AND N-ACYLALANYLHYDRAZONE IODIDES

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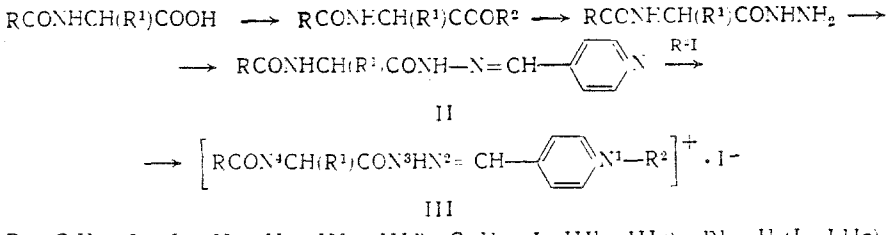
It is known that cationic surface active compounds (SAC) are used in medicine as antibacterial agents [1], but in several cases their use is restricted because of their high toxicity. There are data in the literature indicating that the use of biogenic compounds, including amino acids, as starting materials creates favorable prerequisites for obtaining SAC which are harmless for human beings. Thus, for example, it is known [2] that salts of higher esters of amino acids have high antimicrobial activity but their toxicity is low for warm-blooded animals. There are also reports that certain higher N-acylderivatives of amino acids and their salts are not toxic for warm-blooded animals, and have appreciable antibacterial activity, although the spectrum of their action, like that of other anionic SAC, is restricted [6]. We therefore undertook the synthesis of a series of new cationic SAC based on higher N-acylamino acids, hoping to obtain antibacterial agents with a low toxicity. In particular, we synthesized a series of hydrozones, starting from higher N-acylamino acid hydrazides and pyridine-4-carboxldehyde



II

III

R = C_9H_{19} (Ia, Ic, IIa, IIc, IIIa, IIId), $C_{11}H_{23}$ (I—IIIb, IIIe); R^1 = H (I—IIIc), CH_3 (I—IIIa, b, IIIe); R^2 = CH_3 (IIIa, b, d), C_2H_5 (IIIe).

Lower alkyl esters of N-acylamino acids were obtained by the usual method [5] by using thionyl chloride as catalyst. It should be noted that in some cases, during esterification of higher N-acyl derivatives of amino acids, partial splitting of the acyl group was observed, but this did not appreciably affect the yield of the reaction product. Hydrazinolysis of the alkyl esters of the higher N-acylamino acids obtained was carried out under usual conditions [7] in the presence of 2-2.5-fold excess hydrazine hydrate.

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