SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF SEVERAL 3-SUBSTITUTED SYDNONIMINES*

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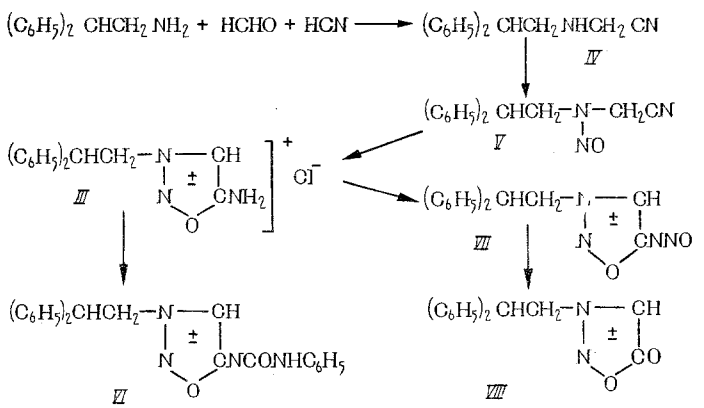
Compounds possessing various pharmacological activity [1, 2] are found in the midst of sydnonimines.

In a continuation of investigations carried out earlier, we carried out the synthesis of several sydnonimine derivatives, and studied the pharmacological properties of the compounds of this series described in this communication and obtained by us earlier [3].

As a supplement to the hydrochlorides of 3-phenoxyethyl-(I)- and 3-(β-hydroxy-β-phenylisopropyl)-(II)-syndnonimines [3], it was of interest to introduce a diphenylmethane group at position 3.

However, investigation of the effect of the substituent (R) in position 3 of the heterocyclic ring [4, 5] on the stability of the sydnonimine hydrochlorides and a study of the mechanism of thermal decomposition of these compounds showed that in the series R equal to $C_6H_5CH_2 \rightarrow C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}H \rightarrow C_6H_5\underset{\displaystyle C_6H_5}{\underset{|}{C}}H$, the stability of the 3-R-sydnonimine hydrochlorides decreases sharply, since in this series the occurrence of the first limiting step of cleavage of the sydnonimine hydrochloride, that of formation of the carbocation R^+, is facilitated. And if 3-benzylsydnonimine hydrochloride is not very stable at room temperature and 3-(α-phenylethyl) sydnonimine hydrochloride can be stored only several days at 3-5°C, then 3-(diphenylmethyl) syndonimine hydrochloride, in general, cannot be stable. At the same time, if the N_3 atom of the heterocyclic ring is separated from the diphenylmethane group by a methylene chain, then the obtained 3-(β,β-diphenylethyl) sydnonimine hydrochloride (III) must be relatively stable, since in this case, the cleavage must proceed as for 3-(β-diphenylethyl) sydnonimine hydrochloride, by another mechanism and significantly slower than for compounds of the series [6] mentioned above. Synthesis of (III) was accomplished by the usual way. Starting from β,β-diphenylethylamine (obtained by hydrogenation of diphenylacetonitrile [7]), the nitrile of N-(β,β-diphenylethyl)-aminoacetic acid (IV) was obtained by the cyanomethylation reaction:



the nitroso derivative (V) of which was converted to the hydrochloride (III) by reaction with hydrogen chloride. Compound (III) was actually found to be stable. Reaction of it with phenylisocyanate yielded the N-exophenylcarbamoyl derivative (VI). Upon reaction with sodium nitrite and an aqueous solution of (III),

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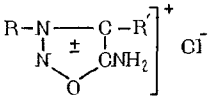
a mixture of the N-exonitroso derivative (VII) and the nitrite of 3-(β,β-diphenylethyl) sydnonimine was formed. Carrying out the nitrosation reaction of (III) in dilute acidic solution avoids the formation of the nitrite and compound (VII) is obtained in high yield. By briefly heating in dimethylformamide [8], the nitroso derivative (VII) was converted to 3-(β,β-diphenylethyl) sydnone (VIII). Under these conditions, the nitrite of 3-(β,β-diphenylethyl) sydnonimine is cleaved to the nitroso derivative (V).

3-(β,β-Diphenylisopropyl) sydnonimine hydrochloride (IX) was synthesized analagously to the preparation of synonimine (III), but without isolation and purification of intermediate compounds, and the nitrile of N-methyl-α-aminoundecanoic acid was synthesized from methylamine hydrochloride, potassium cyanide, and n-decylaldehyde, and 3-methyl-4-(n-nonyl) sydnonimine hydrochloride (X) was synthesized from it by the usual method. In analogy with 9-carboxyethylsydnonimine hydrochloride obtained by us earlier [9], 3-(γ-carboxypropyl) sydnonimine hydrochloride (XI) was synthesized starting from γ-aminobutyric acid (GABA). Cyanomethylation of GABA was carried out in weakly basic medium, using the bisulfite derivative of formaldehyde instead of formalin. The amino nitrile was subjected to nitrosation without isolation, and the water-soluble nitroso derivative was recovered by multiple extraction with ether and then without purification closed to the sydnonimine (XI) with hydrogen chloride.



For I — III, IX, XI — XIV R′ = H. I R=$C_6H_5OCH_2CH_2$. II R=$C_6H_5CHOHCHCH_3$.

III R = $(C_6H_5)_2CHCH_2$. IX R = $(C_6H_5CH_2)_2CH$- X R = CH_3, R′ = н-C_9H_{18}.

XI R = $HOOCCH_2CH_2CH_2$. XII R = $CH_3COOCH_2CH_2$. XIII R = $CH_3CH_2CHCH_3$.

XIV R = $CH_3(CH_2)_5CHCH_3$.

It was possible to acetylate only the hydroxy group in almost quantitative yield and not affect the exocyclic imino group upon reaction of acetic anhydride with 3-(β-hydroxyethyl) sydnonimine hydrochloride [9] in the cold in the presence of catalytic amounts of hydrogen chloride to give 3-(β-acetoxyethyl) sydnonimine hydrochloride (XII).

The pharmacological properties of the sydnonimine hydrochlorides synthesized in this work (III and IX) and earlier [3] (I, II, XIII, XIV) were studied.

In the study of pharmacological properties of the indicated 3-substituted sydnonimines, it was established that they all are of low toxicity. Thus, in experiments on mice upon intraperitoneal introduction, the LD_{50} for compounds (II), (III), (IX), (XIII), and (XIV) amounts to 225, 212, 107.5, 175, and 98 mg/kg, respectively; the toxicity of compounds (I) and (XI) was investigated under intravenous introduction, and their LD_{50} amounts to 75 and less than 400 mg/kg, respectively.

Compounds (II), (III), (IX), (XIII), and (XIV) cause a peripheral adrenopositive effect and a stimulating effect on the central nervous system. In experiments on narcotized cats, they cause an increase in the arterial pressure and constriction of the third musculus palpebralis tertius in a dose of 3-5 mg/kg intravenously. Adrenolytic compounds eliminated these effects, but ganglion blockers did not change them. A noticeable pressure effect of the compounds was very variable—from insignificant to a stable pressure increase of 20-30 mm of Hg. The stimulating effect of these compounds on the central nervous system showed up by an increase in the reflector excitability of mice and rats upon interperitoneal introduction; the stimulating effect of compounds (III) and (XIV) appeared in doses amounting to 1/3-1/2 LD_{50}, and in (II), (IX), and (XIII), in doses equal to 1/5-1/4 LD_{50}. In addition, compounds (II), (IX), and (XIII) caused a brief increase of the motor activity of the animals; panting, exophthalmia, and piloerection. Compounds (II) and (III) increased the rectal temperature of animals by 0.6-1.2°C and slightly strengthened the convulsion effect of 5-hydroxytryptophane, causing the appearance of a phenamino-like effect of β-phenylethylamine.

The effect of 3-β-phenoxyethylsydnonimine hydrochloride (I) differed significantly from the effect of the other compounds. In fine experiments on cats, intravenous introduction of this material in a dose of 10-20 mg/kg caused a lowering of the arterial pressure by 30-50 mm for 1-2 h., simultaneously, a moderate but persistant reduction of the third musculus palpebralis tertius was observed. In parallel with the

hypotensive effect of the compound, the pressure reaction and the musculus palpebralis tertius reaction upon introduction of adrenalin clearly decreased; compound (I) did not cause a noticeable effect on the central nervous system.

3-γ-Carboxypropylsydnonimine hydrochloride (XI), a derivative of GABA, proved to be a low-activity compound; in particular, upon intravenous introduction into mice in a dose of 200 mg/kg, the length of hexenal sleep and the analgesic effect of promedol did not change.

The results of pharmacological investigations indicate that it should be considered expedient to carry out a further study of the 3-alkyl and 3-aralkyl substituted sydnonimine series, with the purpose of searching for compounds having an effect on the central nervous system and peripheral adrenoreactive structures.

EXPERIMENTAL

Nitrile of N-(β,β-Diphenylethyl)-α-aminoacetic Acid (IV). To a solution of 23.3 g (0.1 mole) of β,β-diphenylethylamine hydrochloride [7] in 100 ml of 50% alcohol was added at 10-15°C 9 g of a 32% solution of formalin and dropwise a solution of 7.8 g (0.12 mole) of potassium cyanide in 40 ml of 50% alcohol. To the mixture was added 100 ml of dichloroethane and stirring was carried out for 2 1/2 h. The organic layer was separated, the solvent was evaporated in vacuum to dryness, and 9 g (38.1%) of nitrile (IV) was obtained, mp 171-172°C (from a mixture of dichloroethane-methanol, 1:1). Found, %: Cl 81.28; H 6.60; N 11.74. $C_{16}H_{16}N_2$. Calculated, %: Cl 81.36; H 6.78; N 11.86.

N-Nitroso-N-(β,β-diphenylethyl)-α-aminoacetonitrile (V). Cyanomethylation was carried out as described above, and after maintaining for 2 1/2 h, the mixture was acidified to Congo with concentrated hydrochloric acid, a solution of 6.9 g (0.1 mole) of sodium nitrite in 35 ml of 50% alcohol was added at 4-6°C, and the reaction mixture was left overnight; the dichloroethane layer was separated, dried with magnesium sulfate, concentrated in vacuum, and the formed precipitate was filtered to give 14 g of nitroso derivative (V) (52.8%), mp 90-91°C, (from abs. alcohol). Found, %: C 72.39; H 5.62; N 15.85. $C_{16}H_{15}N_3O$. Calculated, %: C 72.40; H 5.61; N 15.84.

3-(β,β-Diphenylethyl) sydnonimine Hydrochloride (III). To a solution of 14.23 g (0.054 mole) of nitrosonitrile (V) in 100 ml of dry methylene chloride at 0-2°C was added 30 ml of an alcoholic solution of hydrogen chloride. The formed precipitate was filtered to give 12.5 g (yield 77.2%), mp 188-189°C (dec., precipitated from abs. alcohol with ether). Found, %: C 63,73; H 5.33; N 13.59; Cl 11.99. $C_{16}H_{16}N_3OCl$. Calculated, %: C 63.68; H 5.31; N 13.93; Cl 11.77.

Reaction of Sodium Nitrite and 3-(β,β-Diphenylethyl) sydnonimine. A. To a suspension of 1.5 g (0.005 mole) of sydnonimine hydrochloride (III) in 30 ml of water was added 1 ml of a 10% solution of hydrochloric acid and 1.9 g of sodium nitrite was added in portions, maintaining the pH at about 7.0. Three hours after addition, the precipitate was filtered and washed on the filter with acetone; 0.62 g of the nitrite of 3-(β,β-diphenylethyl) sydnonimine was obtained. Found, %: Cl 61.76; H 5.17; N 18.00. $C_{16}H_{16}N_4O_3$. Calculated, %: C 61.54; H 5.13; N 17.95.

The N-nitroso derivative (VII) was precipitated from the acetone mother solution with water, yield 0.47 g, mp 116-117°C (from methanol). Found, %: C 65.20; H 4.77. $C_{16}H_{14}N_4O_2$. Calculated, %: C 65.36; H 4.76.

B. To a suspension of 3 g of sydnonimine (III) in 450 ml of water was added 1 ml of a 10% solution of hydrochloric acid and 2.9 g of sodium nitrite. After 20 h, the precipitate was filtered; yield of N-nitroso derivative of sydnonimine (VII) was 2.35 g (80.6%), mp 116-117°C (from methanol).

Thermal Cleavage of the Nitrite of 3-(β,β-Diphenylethyl) sydnonimine. A solution of 0.62 g of the nitrite of 3-(β,β-diphenylethyl) sydnonimine in 4 ml of dimethylformamide was heated on a boiling water bath for 10 min and after cooling 0.11 g of N-nitroso-N-(β,β-diphenylethyl)-α-aminonitrile (V), mp 90-91°C (from abs. alcohol), was precipitated with water. The material does not give a melting point depression in a mixed sample with authentic (V).

3-(β,β-Diphenylethyl) sydnone (VIII). A solution of 1 g of the N-nitroso derivative of 3-(β,β-diphenylethyl) sydnonimine in 5 ml of dimethylformamide was heated on a boiling water bath for 1 h, the solvent was distilled in vacuum at 40-45°C, and after trituration with ether, sydnone (VI) was filtered, mp 141-142°C (from abs. alcohol). Found, %: C 71.57; H 5.10; N 10.45. $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.18; H 5.26; N 10.53.

N-Phenylcarbamoyl-3-(β,β-diphenylethyl) sydnonimine (VI). To a solution of 0.67 g (0.0022 mole) of sydnonimine (III) in 15 ml of methanol cooled to 0°C were added 0.18 g (0.0022 mole) of fused sodium acetate and 0.44 ml of phenylisocyanate. After maintaining for 2 days, the mixture was filtered, the mother solution was evaporated under vacuum, and the residue was triturated with ether and washed with water to give 0.34 g (48%), mp 132-133°C (from alcohol). Found, %: N 14.6. $C_{23}N_{20}N_4O_2$. Calculated, %: N 14.6.

3-(β,β-Diphenylisopropyl) sydnonimine Hydrochloride (IX). To a solution of 4 g (0.016 mole) of β,β-diphenylisopropylamine hydrochloride in 24 ml of 50% alcohol were added 4 ml of formalin and, with cooling, a solution of 0.8 g of potassium cyanide in 10 ml of 50% alcohol; the mixture was stirred for 3 h, made acidic to Congo with concentrated hydrochlorid acid, and nitrosated with a solution of 1.68 g (0.024 mole) of sodium nitrite in 10 ml of water. After maintaining for an hour, the separated oil was extracted with ether, dried with magnesium sulfate, and treated at 0-2°C with 10 ml of a 4 N ether solution of hydrochloric acid. We obtained 1.5 g (IX; 29.8%), mp 167-168°C (precipitated from abs. alcohol with abs. ether). Found, %: C 64.17; H 5.70; N 13.29; Cl 11.10. $C_{17}H_{18}ClN_3O$. Calculated, %: C 64.76; H 5.71; N 13.35; Cl 10.13.

Hydrochloride of the Nitrile of N-Methyl-α-aminoundecanoic Acid. To a solution of 0.05 mole of methylamine hydrochloride in 10 ml of water was added 8 ml of decyl aldehyde and dropwise at 10-15°C a solution of 0.055 mole of potassium cyanide in 5 ml of water; after maintaining for 20 h and acidifying, the precipitate was filtered to yield 2.7 g (23.3%), mp 121-122°C (from acetone). Found, %: C 61.96; H 10.74; Cl 15.24. $C_{12}H_{25}N_2Cl$. Calculated, %: C 61.98; H 10.77; Cl 15.55.

3-Methyl-4-nonylsydnonimine Hydrochloride (X). To a solution of 2 g (0.1 mole) of the hydrochloride of the nitrile described above in 10 ml of water cooled to 2-4°C was added a solution of 0.7 g of sodium nitrite in 3 ml of water. After maintaining for 2 h, the nitrosonitrile was extracted with ether. The dried extract was treated with ethereal HCl to give 1.6 g (61.7%), mp 121-122°C (from acetone). Found, %: C 55.07; H 9.02; Cl 12.88. $C_{12}H_{24}N_3OCl$. Calculated, %: C 55.07; H 9.18; Cl 13.57.

3(γ-Carboxypropyl) sydnonimine Hydrochloride (XI). To a solution of 1.76 g (0.02 mole) of γ-aminobutyric acid in 5 ml of water were added 0.8 g (0.02 mole) of sodium hydroxide in 7.5 ml of water and 2.9 g (0.02 mole) of the bisulfite derivative of CH_2O in 5 ml of water. After 1/2 h at 15°C a solution of 1.35 g of potassium cyanide in 5 ml of water was added. The mixture was stirred for 2 h at room temperature and left for 20 h. The mixture was acidified with concentrated hydrochloric acid to an acid reaction to Congo and a solution of 2 g of sodium nitrite in 6 ml of water was added at 2-4°C; after maintaining for an hour at 10-12°C the product was extracted with ether and dried with magnesium sulfate. At 4-6°C was added 6 ml of a 4 N ether solution of HCl and the mixture was left for 20 h. The precipitate was filtered and 0.5 g of sydnonimine (XI) was obtained, mp 125-127°C (dec., from butanol). Found, %: C 34.81; H 4.72; N 20.01; Cl 16.93. $C_6H_{10}N_3O_3Cl$. Calculated, %: C 34.70; H 4.82; N 20.24; Cl 17.10.

3-(β-Acetoxyethyl)sydnonimine Hydrochloride (XII). A mixture of 0.82 g of 3-(β-hydroxyethyl)sydnonimine hydrochloride [9], 2.5 ml of acetic anhydride, and 0.1 ml of an alcoholic solution of hydrogen chloride was left for two days at room temperature. The formed precipitate was filtered and additional compound was precipitated from the mother solution with acetone. Yield 1.02 g (95%), mp 129-129.5°C (dec., from acetonitrile). Found, %: C 34.58; H 4.64; Cl 17.24. $C_6H_{10}ClN_3O_3$. Calculated, %: C 34.70; H 4.82; Cl 17.11. UV spectrum (in alcohol): λ_{max} 260 and 301 mμ, log ε 4.07 and 3.45. IR spectrum: $\nu_{C=O}$ 1740 cm^{-1}, $\nu_{C=N}$ 1684 cm^{-1}, ν_{NH_2} 1608 cm^{-1}.

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