# PHENYLETHYL DERIVATIVES OF SYDNONE IMINES

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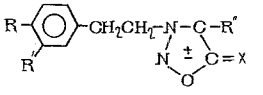
UDC 615.31:547.415.3

Substances which exert a psychotropic action have been found among the sydnone imine derivatives which contain an aralkyl substituent in the third position [1]. The sydnonyl derivatives of phenylisopropylamine have been studied in more detail; one of these – 3-phenylisopropylsydnone imine hydrochloride (I) – under the name "sidnofen" is used as a psychotropic medicine.

Sydnonyl derivatives of the phenylethyl series, which have substituents in the benzene or the heterocyclic rings, present no less interest. From tyramine, O-methyltyramine, and homoveratrylamine, we have synthesized the hydrochlorides of 3-(4'-hydroxyphenylethyl), 3-(4'-methoxyphenylethyl), and 3-(3', 4'-dimethoxyphenylethyl)sydnone imines (II, III, and IV, respectively).



II R=OH, R'=R''=H; X=NH·HCl,
IIa R=O⁻, R'=R''=H; X=$\overset{+}{N}H_2$,
III R=$CH_3O$, R'=R''=H; X=NH·HCl,
IV R=R'=$CH_3O$, R''=H; X=NH·HCl,
V R=R'=H, R''=$CH_3$, X=NH·HCl
VI R=R'=H, R''=$C_6H_5$; X=NH·HCl
VII R=R'=R''=H; X=NH·HCl
VIII R=R'=$CH_3O$, R''=H, X=NCOCH$_3$
IX R=R'=$CH_3O$, R''=H, X=NCONH$C_6H_5$
X R=R'=R''=H; X=3,4,5-$(CH_3O)_3C_6H_2CON$
XI R=R'=R''=H, X=$C_6H_5CON$

Moreover, from phenylethylamine we have prepared the 4-methyl (V) and the 4-phenyl (VI) derivatives of the previously synthesized 3-phenylethylsydnone imine hydrochloride (VII).

In the IR spectra of hydrochlorides II-VI there are characteristic bands in the frequency ranges 1600-1700 and 3100-3500 $cm^{-1}$ (see Table 1, where, for comparison, we give data on compound VII hydrochloride). In the UV spectra of compounds II-VII there are intense absorption maxima which are characteristic of sydnone imine salts (see Table 1).

In connection with data available in the literature [2] on the possibility that sydnone imines exist in the form of internal salts, we attempted to prepare the internal salt from hydrochloride II by the action of sodium bicarbonate in aqueous solution at low temperature. Thereupon there was isolated a finely crystalline powder of light yellow color – a substance which did not contain chloride ion nor a nitroso group (Liebermann test). Its IR spectrum proved close to the spectrum of II hydrochloride, only the absorption bands for the C≡N frequency and $\delta_{NH}$ (1680 and 1615 $cm^{-1}$) of the compound obtained were shifted somewhat into the long wavelength region; the band at 3195 $cm^{-1}$ indicates the presence of a sydnone imine ring having a hydrogen in the fourth position. On the basis of these data and the analytical results, this compound was assigned the structure of the internal salt (IIa). In its UV spectrum, just as in that of II hydrochloride, there are two short-wave maxima; however the third is shifted somewhat in the short wavelength direction (Fig. 1).

The N-exo-acetyl (VIII) and N-exo-carbamoyl (IX) derivatives were prepared from IV hydrochloride by the usual methods; and the N-exo-3',4',5'-trimethoxybenzoyl (X) and N-exo-benzoyl (XI) derivatives were prepared from VII hydrochloride. Similarly, N-exo-3', 4', 5'-trimethoxybenzoyl-3-phenylisopropylsydnone imine (XII) was prepared from I hydrochloride.

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TABLE 1. Data from IR and UV Spectra of Sydnone Imines

| Compound | $\nu_{C=N}$ | $\nu^{+}_{NH}$ | $\sigma^{+}_{NH}$ | $\nu_{C_4-H}$ | $\lambda_{max}$ (in mμ) | lg ε | Compound | $\nu_{C=N}$ | $\nu^{+}_{NH}$ | $\sigma^{+}_{NH}$ | $\nu_{C_4-H}$ | $\lambda_{max}$ (in mμ) | lg ε |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | cm$^{-1}$ | | | | | | | cm$^{-1}$ | | | | | |
| II | 1690 | 3340 | 1620 | 3160 | 203 | 4,20 | VII | 1679 | 3350 | 1590 | 3180 | 208 | 4,28 |
| | | 3435 | | | 226 | 3,81 | | | | | | 298 | 4,08 |
| III | 1700 | 3340 | 1620 | 3160 | 292 | 3,87 | VIII | 1555 | 1627 | — | 3130 | 203 | 4,59 |
| | | | | | 202 | 4,44 | | | $\nu_{CO}$ | | | 237 | 4,12 |
| IV | 1712 | 3340 | 1620 | 3180 | 225 | 4,02 | | | | | | 325 | 4,06 |
| | | | | | 296 | 3,87 | IX | 1540 | 1650 | — | 3180 | 204 | 4,80 |
| V | 1680 | 3342 | 1630 | — | 206 | 4,54 | | | | | | 260 | 4,59 |
| | | 3435 | | | 220 | 3,90 | X | 1560 | 1620 | — | 3168 | 342 | 4,18 |
| VI | 1678 | 3340 | 1613 | — | 293 | 3,89 | | | | | | 215 | 4,54 |
| | | | | | 208 | 4,29 | XI | 1570 | 1628 | — | 3168 | 273 | 4,06 |
| | | | | | 306 | 4,20 | | | | | | 340 | 4,62 |
| | | | | | 206 | 4,35 | | | | | | 200 | 4,64 |
| | | | | | 247 | 3,90 | | | | | | 258 | 4,23 |
| | | | | | 315 | 3,93 | | | | | | 335 | 4,52 |

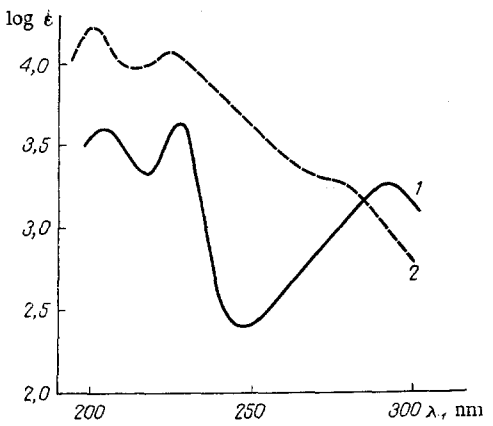


Fig. 1. UV Spectra (in alcohol). 1) 3-(4'-hydroxyphenylethyl)sydnone imine hydrochloride (II); 2) internal salt of the foregoing (IIa).

Two absorption bands are absorbed in the IR spectra of the acyl derivatives VIII-XI in the 1500-1700 cm$^{-1}$ region, one of which (1540-1570 cm$^{-1}$) should be assigned to the valence stretching vibrations of the C=N bond; and the other (1620-1650 cm$^{-1}$), to the valence stretching bands of the C=O bond. The band at 3130-3180 cm$^{-1}$ corresponds to the $C_4$—H vibrations. The UV spectra of the N-aroyl derivatives (X, XI) in alcohol are characterized by the presence of three absorption maxima (Fig. 2).

With the objective of revealing ability for salt formation, we took the spectra of these compounds in alcoholic hydrogen chloride solution. For compound X, hardly any changes in the spectrum were detected; however, the spectrum of the benzoyl derivative changed somewhat. In 3 N hydrochloric acid the absorption maximum of the latter compound was sharply shifted into the short wavelength region. The UV spectra of derivatives X and XII, due to poor solubility, could not be taken under these conditions. It is probable that, in distinction from the benzoyl derivative, the trimethoxybenzoyl derivative is not capable of forming a hydrochloride, apparently because of reduced basicity of the exocyclic nitrogen atom.

Results of pharmacological investigation of most of the compounds synthesized showed that among them there are substances which affect the central nervous system and which exert a peripheral sympathomimetic action. Upon introduction of VII hydrochloride subcutaneously or intraperitoneally into white mice or rats in a dose of 25-50 mg/kg, reflector irritability is sharply intensified, and it causes an aggressive state in the animals plus stereotyped movements similar to phenamine stereotypy. The preparation somewhat reduces the sedative and hypothermic action of reserpine, and intensifies the convulsive effect of tryptamine and 5-hydroxytryptophan. These properties of the preparation can be caused to a definite degree by its anti-monoaminooxidase activity [1]. In acute experiments on cats, the preparation (3-5 mg/kg, intravenously) causes an elevation of arterial pressure and clearly intensifies the pressor effect of adrenalin and noradrenalin. The $LD_{50}$ of compound VII in venous introduction into mice is 92 mg/kg.

Compounds II, III, IV, and VIII are similar in action to VII; however, they are less toxic. Intravenous injection of the preparations in a dose of 100 mg/kg does not cause death of mice; a transient adinamy, respiratory depression, and sometimes mild clonic convulsions are observed in the animals. Compounds II and III, starting at a dose of 50 mg/kg, upon intravenous injection cause an elevation of reflector irritability in part of the animals and intensify the convulsant action of tryptamine or 5-hydroxytryptophan. The hydrochloride of IV exerts a similar action in a dose of 100 mg/kg. In this same dose, compound VIII does not change the reflector irritability of mice and only slightly intensifies the convulsant effect of 5-hydroxytryptophan.

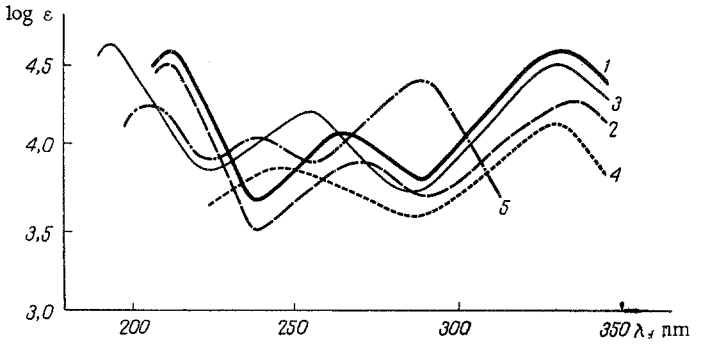


Fig. 2. UV spectra of N-exo-(3', 4', 5'-trimethoxybenzoyl)-3-phenylethylsydnone imine (X) (1, 2) and of N-exo-benzoyl-3-phenylethylsydnone imine (XI) (3, 4, 5). 1) In alcohol; 2) in alcoholic hydrogen chloride solution; 3) in alcohol; 4) in alcoholic hydrogen chloride solution; 5) in 3 N hydrochloric acid.

In acute experiments on cats compounds II-IV and VIII in a dose of 3-5 mg/kg cause a slight elevation of arterial pressure and somewhat increase the duration of the pressor action of adrenalin or noradrenalin.

Compounds IX and X were introduced into animals by mouth in the form of an aqueous suspension. In a dose of 100 mg/kg the latter did not display any activity in experiments on mice or rats. Compound IX in this dose caused activation of behavioral reactions in animals.

Thus, the results of the pharmacological studies performed have shown that the introduction of hydroxy or methoxy groups into the benzene ring of phenylethyl derivatives of sydnone imines leads to a reduction of both the central and the peripheral sympathomimetic activity of the compounds.

## EXPERIMENTAL

3-(4'-Hydroxyphenylethyl)sydnone Imine Hydrochloride (II). To a solution of 0.24 g of the sodium bisulfite–formaldehyde compound in 10 ml of water was added 1 g of tyramine and 0.5 g of potassium cyanide, at 10°. After 2 h there had separated 0.81 g of N-(4'-hydroxyphenylethyl)aminoacetonitrile (XIII), mp 118-119° (from water). Found, %: C 68,34; H 6.81; N 15.61. $C_{10}H_{12}N_2O$. Calculated, %: C 68.16; H 6.89; N 15.89.

To a solution of 0.42 g of XIII in 5 ml of methanol at pH 3.0 was added a solution of 0.14 g of sodium nitrite in 2 ml of water, and the mixture was extracted with ether. The dried ether solution was treated with 5 ml of an ethereal hydrogen chloride solution, and the precipitate which settled was twice reprecipitated from methanol with absolute ether; 0.29 g of II hydrochloride was obtained, mp 178-179° (decomp.). Found, %: C 49, 10; H 5.24; N 17.40; $Cl^-$ –14.59. $C_{10}H_{11}N_3O_2 \cdot HCl$. Calculated, %: C 49.23; H 5.34; N 17.40; $Cl^-$ –14.61.

To a solution of 1.85 g of II hydrochloride in 30 ml of water at -5° was added 0.65 g of sodium bicarbonate. The precipitate which had separated after 2 h was recrystallized from 8% aqueous alcohol, and 0.85 g of the sydnone imine internal salt (IIa) was obtained, mp 72-73°. Found, %: C 58.11; H 5.19; N 20.59. $C_{10}H_{11}N_3O_2$. Calculated, %: C 58.55; H 5.45; N 20.48.

3-(4'-Methoxyphenylethyl)sydnone Imine Hydrochloride (III). Analogously to XIII, from 4.7 g of O-methyltyramine there was obtained 2.35 g of N-(4-methoxyphenylethyl)aminoacetonitrile, in the form of the hydrochloride, mp 157-158° (from isopropyl alcohol). Found, %: C 58.49; H 6.87; N 12.78; $Cl^-$ 15.62, $C_{11}H_{14}N_2O \cdot HCl$. Calculated, %: C 58.30; H 6.66; N 12.31; $Cl^-$ 15.65. The hydrochloride obtained (2.2 g) was nitrosated by the action of 0.7 g of sodium nitrite in 5 ml of water; after 2 h at pH 3.0 the mixture was extracted with ethyl acetate and the dried extract was treated with an ethereal hydrogen chloride solution. There was obtained 1.05 g of III hydrochloride, mp. 147-148° (decomp., precipitated from alcohol by ether). Found, %: C 51.85; H 5.44; N 16.32; $Cl^-$ –14.33. $C_{11}H_{13}N_3O_2 \cdot HCl$. Calculated, %: C 51.80; H 5.54; N 16.41; $Cl^-$ 13.85.

3-(3', 4'-Dimethoxyphenylethyl)sydnone Imine Hydrochloride (IV). From 2.5 g of homoveratrylamine, by the cyanomethylation and nitrosation reactions, there was synthesized 1.47 g of N-nitroso-N-(3, 4-dimethoxyphenylethyl)aminoacetonitrile, mp 84-85° (from absolute alcohol). Found, %: C 58.23; H 6.79; N 16.81. $C_{12}H_{15}N_3O_3$. Calculated, %: C 58.10 H 6.60; N 16.85.

The nitrosonitrile (1 g) was treated with an ethereal hydrogen chloride solution, and there was obtained 0.95 g of IV hydrochloride, mp 150-150.5° (from absolute alcohol). Found, %: C 50.69; H 5.66; N14.69; $Cl^-$ 12.43. $C_{12}H_{15}N_3O_3 \cdot HCl$. Calculated, %: C 50.50; H 5.62; N 14.71; $Cl^-$ 12.45.

3-Phenylethyl-4-methylsydnone Imine Hydrochloride (V). This was prepared like compound II, from phenylethylamine and the sodium bisulfite compound of acetaldehyde (with isolating the intermediate aminonitrile); yield, 25% (based on phenylethylamine), mp 170-171° (decomp., from isopropyl alcohol). Found, %: C 54.85; H 5.98; $Cl^-$ 14.84. $C_{11}H_{13}N_3O \cdot HCl$. Calculated, %: C 55.02; H 5.90; $Cl^-$ 14.81.

3-Phenylethyl-4-phenylsydnone Imine Hydrochloride (VI). From 10 g of phenylethylamine, 4.65 g of potassium cyanide, and 6.75 g of benzaldehyde there was obtained 9.53 g of N-phenylethylaminophenylacetonitrile, mp 68-69° (from isopropyl alcohol). Found, %: C 81.03; H 6.52, $C_{16}H_{16}N_2$. Calculated, %: C 81.40; H 6.80. In a manner like that of preparation of II, from 8 g of this nitrile there was synthesized 2.61 g of VI hydrochloride, mp 143-143.5° (decomp., from absolute alcohol). Found, %: C 63.57; H 5.48; N 13.62; $Cl^-$ 11.61. $C_{16}H_{15}N_3O \cdot HCl$. Calculated, %: C 63.70; H 5.32; N 13.19; $Cl^-$ 11.79.

N-exo-Acetyl-3-(3', 4'-dimethoxyphenylethyl)sydnone Imine (VIII). This compound was obtained by treating IV hydrochloride with acetic anhydride in the presence of sodium acetate, with subsequent evaporation of the filtered reaction mixture, mp 137-139° (from acetone). Found, %: C 57.90; H 5.83; N 14.04. $C_{14}H_{17}N_3O_4$. Calculated, %: C 57.90; H 5.85; N 14.40.

N-exo-Phenylcarbamoyl-3-(3', 4'-dimethoxyphenylethyl)sydnone Imine (IX). From 4 g of IV hydrochloride and 2.2 ml of phenyl isocyanate in the presence of 1.4 g of sodium bicarbonate there was obtained 2.67 g of IX, mp 134.0-134.5° (from methanol). Found, %: N 15.48. $C_{19}H_{20}N_4O_4$. Calculated, %: N 15.52.

N-exo-(3', 4', 5'-Trimethoxybenzoyl)-3-phenylethylsydnone Imine (X). To a solution of 2.5 g of VII hydrochloride in 50 ml of water at 0° was added 2.55 g of 3, 4, 5-trimethoxybenzoyl chloride and 5 g of sodium bicarbonate. After 3 h, 3.47 g of X was isolated, mp 170-171° (from 50° alcohol). Found, %: C 62.40; H 5.42; N 11.14. $C_{20}H_{21}N_3O_5$. Calculated, %: C 62.65; H 5.52; N 10.96.

N-exo-(3', 4', 5'-Trimethoxybenzoyl)-3-phenylisopropylsydnone Imine (XII). This compound had mp 138-139° (from 80% methanol). Found, %: C 63.60; H 5.85; N 10.54. $C_{21}H_{23}N_3O_5$. Calculated, %: C 63.40; H 5.85; N 10.58. $\lambda 2^{weak}_{max}$ 15, 273, and 340 nm; log ε, 4.35, 3.54, and 4.25, respectively.

N-exo-Benzoyl-3-phenylethylsydnone Imine (XI). mp 149-150° (from 50% alcohol). Found, %: C 69.59; H 5.16; N 14.61. $C_{17}H_{15}N_3O_2$. Calculated, %: C 69.60; H 5.12; N 14.35.

Compounds XI and XII were synthesized like X.

The IR spectra were taken in a thin layer of Vaseline oil in an IR-10 instrument; the UV spectra, in an MPS 50 instrument; d, 1 cm; C, $1 \times 10^{-4}$ to $1 \times 10^{-5}$ moles/liter.

## LITERATURE CITED


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