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The Chemistry of Sydnone Imines

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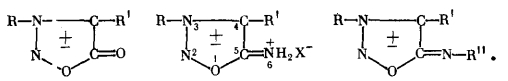
All the available data on the structures, physicochemical properties, reactivities, reactions, and biological activities of sydnone imines—representatives of the class of the so-called mesoionic heterocycles—are surveyed and described systematically.
The bibliography includes 166 references.

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I. INTRODUCTION

Among the so-called mesoionic heterocyclic compounds[1-4], sydnones (I), which are derivatives of anhydro-1,2,3-oxadiazol-5-one, are best known and have been most thoroughly investigated. Their exocyclic nitrogen analogues—the sydnone imines (II) and (III)—were discovered only 20 years ago, but during these years many interesting data have been obtained on the structures, reactivities, physicochemical properties and biological activities of these compounds.



(I) (II) (III)

Certain representatives of sydnone imines have found application as medicinal drugs. Soviet and Japanese investigators have made the greatest contribution to the development of this interesting field of the chemistry of heterocycles.

While the chemistry of sydnones has been fairly widely described in the review literature[2,3], only brief information is available concerning their nitrogen analogues—sydnone imines. This article is the first attempt at a survey and systematic account of data on the synthesis, structures, and chemical, physical, and biological properties of sydnone imines available in the periodical and patent literature (up to 1978 inclusive).

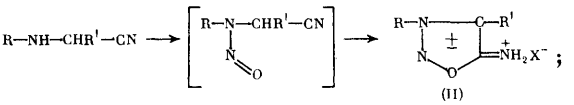
II. THE SYNTHESIS OF SYDNONE IMINES

Sydnone imines exist in the form of salts, as a rule hydrochlorides (II, X = Cl), or exocyclic derivatives ($N_{(6)}$-derivatives) (III), where R" are the residues of various organic acids (carboxylic, carbamic, arenesulphonic etc.) or inorganic acids (nitrous, nitric etc.). With the exception of special cases (see below), sydnone imines have not been isolated in the form of the free base.

1. Sydnone Imine Salts

Although the possibility of the existence of nitrogen analogues of sydnones was predicted as early as 1949,[5] the first sydnone imines were synthesised in 1957 independently by Japanese[6] and English[7] chemists.

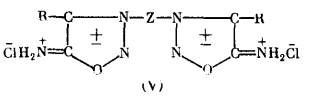
Having treated *N*-nitroso-*N*-phenylaminoacetonitrile (IVa) and its *C*-phenyl analogues (IVb) with hydrogen chloride, Kato et al.[6] obtained the hydrochlorides of 3-phenylsydnoneimine (IIa) and 3,4-diphenylsydnoneimine (IIb). When the *N*-methyl derivatives of isobutyronitrile and isovaleronitrile were treated with nitrogen oxides, the corresponding sydnone imines (II, c and d) were isolated in the form of the hydrogen nitrates (X = NO_3), which were then converted into the hydrochlorides (X = Cl):[7]



(II)

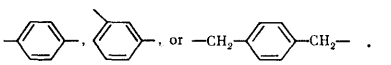
(a) R = C_6H_5, R' = H; (b) R = R' = C_6H_5;
(c) R = CH_3, R' = iso-C_4H_9; (d) R = CH_3, R' = iso-C_5H_{11}.

A large number of sydnone imine salts with various substituents in the 3- and 4-positions in the ring have been synthesised by the cyclisation of *N*-substituted *N*-nitroso-α-aminonitriles (IV) in an acid medium (the only known method hitherto). Derivatives of sydnones themselves and their exocyclic hydrogen analogues with an unsubstituted third nitrogen atom do not exist. The majority of the known sydnone imines contain hydrocarbon substituents in the 3-position: alkyl,[7,8-18] cycloalkyl,[9,10,19,20] arylalkyl,[9,11-15,17,21-23,25,26] and aryl.[6,9,11,17,27] Polymethylene-3,3'-bis-sydnone imines[9,28,29] and phenylene-3,3'-bis-sydnone imines (V)[9,16,30] have been described:



(V)

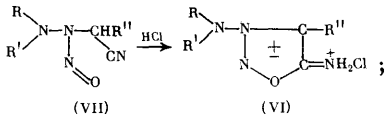
Z = $(CH_2)_n$ (*n* = 2-10), $(CH_2)_2$—O—$(CH_2)_2$,



Sydnone imines containing various functional and other groups in the hydrocarbon substituent have been synthesised, for example: 3-hydroxyethyl[14], 3-chloroethyl[14], 3-carboxylalkyl[31,32], 3-alkoxycarbonylalkyl[33], 3-dialkylaminoalkyl[34], and dinitromethyl-3,3'-bisethyl[35] derivatives. The presence of powerful electronegative substituents (for example, three nitro-groups[35]) in the β-position of the hydrocarbon chain attached to the nitrogen atom prevents cyclisation with formation of a mesoionic heterocycle.

N-nitrosoaminoacetonitriles with an arylacetyl or sulphogroup at the amino-nitrogen atom do not enter into the cyclisation reaction[6].

In recent years much attention has been devoted to the synthesis of sydnone imine salts (VI) with a dialkylaminogroup in the 3-position, which are obtained by the cyclisation of *N*-nitroso-derivatives of various *N*,*N*'-dialkyl and *N*,*N*'-cycloalkyl-hydrazinoacetonitriles (VII) under the influence of hydrogen chloride[36–47]:

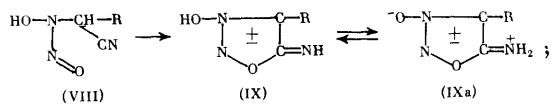


(VII) (VI)

R, R' = alkyls or X, where X = CH_2, O, or NH.

Among sydnone imines of this type, compounds containing the morpholino-,[36–38,44,45] piperidino-,[36,37,40,41,45] piperazino-,[36,45] and *N*'-substituted piperazino-groups[36,38,39,46,47] have attracted most attention.

It has recently proved possible to cyclise derivatives of *N*-nitrosohydroxylaminoacetonitrile (VIII),[48] which yielded 4-alkyl-substituted 3-hydroxysydnoneimines (IX), to which the betaine structure (IXa) was ascribed:

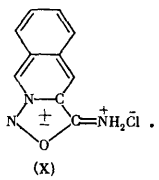


(VIII) (IX) (IXa)

R=C_3H_7, $PhCH_2$, or $PhCH_2CH_2$.

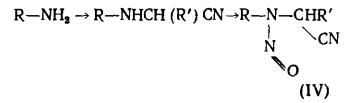
The cyclisation of *N*-nitrosoaminoacetonitriles can give rise to sydnone imine salts containing, apart from hydrogen, hydrocarbon substituents in the 4-position of the ring, namely alkyl[7,9,11–13,16,18,26,31,36,39], arylalkyl and aryl[9,11,12,16,17,25,36], chloromethyl[18,44], and dialkylaminomethyl[44] groups in the 4-position of the ring.

The synthesis of a single representative of the tricyclic series—3,4-dihydroisoquinolinyl[1,2-*c*]sydnone imine hydrochloride—has been described:



(X)

The synthesis of sydnone imine salts is fairly simple and consists in general of three stages: (1) the formation of an *N*-substituted α-aminonitrile having at least one hydrogen atom at the α-carbon atom; (2) the nitrosation of the α-aminonitrile; (3) the cyclisation of the resulting *N*-nitroso-derivative to the sydnone imine:



(IV)

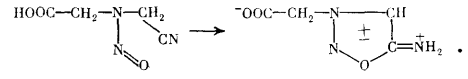
Sometimes the isolation of one or both intermediates is difficult and the synthesis of sydnone imines is converted into a single-stage process; this requires a more careful purification of the final product.

α-Aminoacetonitriles are usually obtained by the cyanomethylation of primary amines. The use of glycolonitrile as the cyanomethylating agent has been described[8]. Acetone cyanohydrin can be conveniently used as the cyanating agent under laboratory and industrial conditions[11,22–24]. Cyanomethyl derivatives of aminoacids can be obtained smoothly in an alkaline medium[14,31–33].

The nitrosation of aminoacetonitriles is carried out in most instances with sodium nitrite in the presence of inorganic acids. When an excess of sodium nitrite in an acid is used, cyclisation can take place in the course of the nitrosation with formation of sydnone imine nitrite or nitrate salts[7,14]. The *N*-nitroso-derivatives (IV) are sometimes obtained in a non-aqueous medium by treating aminotriles with nitrogen oxides.

Other inorganic acids, for example sulphuric, as well as organic carboxylic acids, such as succinic and picric, can be used for the cyclisation of nitrosoaminonitriles (IV) to sydnone imine salts, in addition to hydrogen chloride in varous organic solvents (lower alcohols, ether, tetrahydrofuran, dichloroethane, methylene chloride, chloroform, ethyl acetate, and acetone)[37].

Nitrosoaminoacetonitriles can also be cyclised in an aqueous medium[9,45]. The cyclisation in acetic acid has recently been described[49] and it has been possible for the first time to demonstrate, in relation to *N*-nitroso-*N*-carboxymethylaminoacetonitrile, the feasibility of self-cyclisation catalysed by the protons of the carboxy-group[50]:

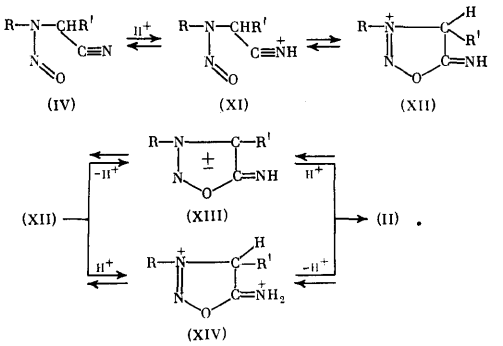


The formation of sydnone imines under the influence of HCl can be accompanied by a side reaction—the denitrosation of *N*-nitrosoaminoacetonitriles with elimination of nitrosyl chloride[14,15,18,26,29]. Thus, despite the variation of the conditions[14], it has not been possible to cyclise *N*-nitroso-*N*-t-butylaminoacetonitrile[14]. The low yields of sydnone imine in the cyclisation of *N*-nitroso-*N*-methylaminoacetonitrile in the presence of an excess of HCl have been noted[18].

It has been suggested[26] that the denitrosation can be avoided by carrying out the cyclisation in solvents without oxygen, for example in methylene chloride; however, it has been shown[15] that the cleavage of nitroso-derivatives and the low yield of sydnone imines are due to the use of an excess of HCl and the increase of temperature above 10 °C rather than the choice of a particular solvent.

A spectrophotometric study of the kinetics of the acid cyclisation of *N*-nitrosoaminoacetonitriles[5] showed that in the case of non-aromatic substituents at the nitrogen atom their reaction is of first order with respect to the nitroso-derivative and of second order with respect to protons. The rate of cyclisation depends significantly on the nature of the substituents at the nitrogen atom of the nitrosoaminoacetonitrile and increases with increasing inductive effect and bulk of the radical. Thus, one passing from the methyl to the cyclohexyl substituent, the rate of cyclisation increases by more than two orders of magnitude. Analysis with the aid of correlation equations made it possible to estimate the electronic and steric effects of the substituents. The equation obtained ($\lg k = -3.2 - 3.6\sigma^* - 1.2E_S^C$) agrees satisfactorily with the experimental cyclisation rate constants. It has been suggested that in the course of this reaction "steric acceleration" takes place with increasing bulk of the substituent at the amino-nitrogen and after the introduction of substituents at the α-carbon atom in the nitrosoaminoacetonitrile. The cyclisation takes place most readily for *N*-nitrosoadamantylaminoacetonitrile: the rate of formation of the sydnone imine ring is in this case more than 1500 times higher compared with the methyl analogue.

From these results, a mechanism of the formation of the sydnone imine ring, illustrated in the scheme below, has been put forward[51]:



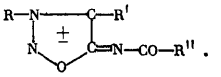
(IV) (XI) (XII) (XIII) (XIV) (II)

The first stage of the process is in all probability the protonation of the nitrile group in (IV) which is followed by the conversion of the protonated product (XI) into the cyclic iminoester diazotate (XII), which can give rise to the cation of the sydnone imine (II) either via the stage of the sydnone imine base (XIII) or via the dication (XIV).

2. *N*-Exocylic ($N_{(6)}$) Derivatives of Sydnone Imines

The exocyclic *N*-derivatives of the heterocycles, which are synthesised from the corresponding salts, have perhaps attracted no less attention than the sydnone imine salts.

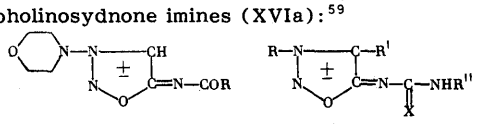
While manifesting properties typical for strong amines, sydnone imine salts interact with carboxylic acid anhydrides and chlorides in the presence of basic agents under mild conditions to form the corresponding $N_{(6)}$-acylsydnone imines (XV):



(XV)

Apart from the $N_{(6)}$-acetyl derivatives (XV, $R = CH_3$),[6,7,10,11,14,21,25,30,32,36,41,48,52-57] which can be prepared by treatment with acetic anhydride in the absence of a base[52], compounds have been synthesised with other alkanoyl[15,53-55] and aroyl[6,10,11,14-16,21,25,36,52,56-58] substituents as well as halogenoacetyl,[53-56] isonicotonyl[15,59], and alkoxycarbonyl[10,11,15,27,36,52,56] groups.

$N_{(6)}$-Acyl derivatives have been obtained not only for sydnone imines with hydrocarbon substituents in the 3- and 4-positions in the ring, but also for 3-hydroxy-,[48] 3-carboxyalkyl-,[32-58] and 3-dialkylamino-derivatives[36,40,41,44,59-63]. By treatment with formic anhydride or *p*-nitrophenyl formate, it has been possible to synthesise the $N_{(6)}$-formyl derivative of 3-morpholinosydnone imines (XVIa):[59]



(XVI) (a) R = H (XVII), X = O (XVIII), X = S

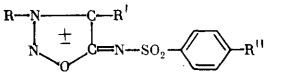
Apart from compound (XVIa), mono-, di-, and tri-chloroacetyl, trifluoroacetyl, phenoxyacetyl, trimethoxybenzoyl, benzyloxycarbonylalanyl, nicotinoyl, and other $N_{(6)}$-acyl derivatives of this sydnone imine have been obtained[59]. The interaction of sydnone imine hydrochlorides with diketen in the presence of sodium dicarbonate yielded $N_{(6)}$-acetoacetylsydnone imines (XV, $R'' = CH_3COCH_2$).[52,54,59]

Sydnone imine salts react smoothly with aliphatic and aromatic isocyanates in the presence of bases—pyridine and sodium acetate or bicarbonate—in aqueous and alcoholic media, forming $N_{(6)}$-carbamoyl derivatives (XVII).[13,15,16,21,32,53-55,58,64-70] Among these, compounds containing carboxy-substituents in the 3-position of the ring have been described[32,58,64].

When the reaction is carried out in an aqueous medium, the corresponding diarylureas are formed by a side reaction in the case of aryl isocyanates. Di-(*o*-chlorophenyl)urea proved to be the only reaction product for *o*-chlorophenyl isocyanate[15]. The reaction takes place most smoothly in alcohols[53,54]. Unsubstituted carbamoyl derivatives (XVII, $R'' = H$) have been synthesised by treating sydnone imine hydrochlorides with sodium cyanate[15,32,64,71,74].

Sydnone imine isothiocyanates react similarly to the isocyanates, giving rise to the corresponding $N_{(6)}$-thiocarbamoylsydnone imines (XVIII).[11,15,52,65] The reaction proceeds under the same conditions as with the oxygen analogues. Unsubstituted thiocarbamoyl derivatives could not be synthesised by treating sydnone imine hydrochlorides with ammonium thiocyanate[15,25,71]. The corresponding sydnone imine hydrogen thiocyanates proved to be the only reaction product.

Several studies have been devoted to the synthesis of $N_{(6)}$-arenesulphonyl derivatives (XIX), which are formed under fairly severe conditions (heating in the presence of aqueous alkali) when sydnone imine salts are acted upon by the corresponding arenesulphonyl chlorides[10,11,59,72,75]:

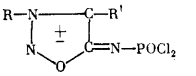


(XIX)

$R'' = H$, $NHCOCH_3$, or NH_2.

The sydnonyl analogues of sulphonamide preparations with the amino-group in the *p*-position in the benzene ring (XIXa, $R'' = NH_2$) have been synthesised in this way[10,72].

When the hydrochlorides of 3-isopropyl-, and 3-phenyl-4-methylsydnone imines were heated cautiously with phosphoryl chloride in dichloroethane solution, the corresponding $N_{(6)}$-dichlorophosphino-derivatives (XX) were synthesised[14]:

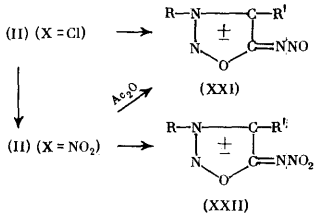


(XX)

$R = C_3H_7$, $R' = H$; $R = Ph$, $R' = CH_3$.

The presence of the exocyclic imino-group is confirmed by the ready formation of $N_{(6)}$-nitroso-derivatives (XXI) when sydnone imine salts are acted upon by sodium nitrite[6,25,32,33,53,73]. A number of $N_{(6)}$-nitroso-derivatives with alkyl, arylalkyl, and aryl substituents in the ring have been synthesised in this way. It has been observed that in certain cases the formation of $N_{(6)}$-nitroso-derivatives requires an acid medium and the introduction of an excess of sodium nitrite in order to avoid the formation of the nitrite of the corresponding sydnone imine[73]. The latter can be converted into $N_{(6)}$-nitrososydnone imine by treatment with acetic

anhydride[73]. The $N_{(6)}$-nitro-derivative (XXII) can be obtained analogously from the sydnone imine nitrite[7]:



(XXI)

(XXII)

III. PHYSICOCHEMICAL PROPERTIES AND ELECTRONIC STRUCTURE

Numerous studies have been made on the physicochemical properties of sydnone imines. Investigation of the ultraviolet, infrared, NMR, and mass spectra, polarographic studies, etc. yielded data which can be used to explain the characteristics of the structures and a number of chemical and physical properties of these heterocyclic compounds. On the other hand, effective methods for the investigation of the kinetics and mechanisms of the chemical reactions of sydnone imines and for the identification of the resulting products have been developed on the basis of the study of certain physicochemical properties.

1. Electronic Spectra

Sydnone imines absorb intensely in the ultraviolet[9,15,27,32,48,52,56,72,73,76-79] and their $N_{(6)}$-nitroso-derivatives have absorption maxima also in the visible part of the spectrum[73]. Alkylsydnone imine salts have two intense absorption maxima in the region of 270–306 and 200–208 nm; the latter has been observed and described quite recently[78].

The bands have been assigned[80] on the basis of quantum-mechanical calculation by the Pariser–Parr–Pople (PPP) method and it has been shown that the long-wavelength maximum is a $\pi-\pi^*$ band corresponding to the $S_0 \rightarrow S_1^*$ transition, while the short-wavelength band corresponds to the $S_0 \rightarrow S_3^*$ transition. Calculations predict[80] the existence of yet another band corresponding to the $S_0 \rightarrow S_2^*$ transition, but, owing to its low intensity, it has not been possible to observe it. The absorption bands of $N_{(6)}$-exonitroso-derivatives of sydnone imines in the visible region have been assigned[73] to the $n \rightarrow \pi^*$ transition.

The nature of the substituents in the 3- and 4-positions in the ring and of the exocyclic group has almost no influence on the position of the short-wavelength maximum, in contrast to the long-wavlenegth absorption, whose shifts reach considerable magnitudes[78]. Thus the introduction of an aryl substituent in the 3- or 4-position in the sydnone imine ring[27] or the substitution of the hydrogen at the exocyclic nitrogen by an aryl residue[27,56] lead to a bathochromic shift of the absorption band and to the appearance of a new band at 222–260 nm. On protonation of $N_{(6)}$-acylsydnone imines, the opposite hypsochromic shift of the long-wavelength band from 308–342 nm to 278–306 nm was observed, which made it possible to measure the pK_a spectrophotometrically[56].

The great similarity of the ultraviolet spectra of sydnone imine salts and correspondingly substituted sydnones, indicating the similarity of the strctures of the electronic shells in these compounds, is striking[76]. A satisfactory correlation of the frequencies of the long-wavelength $\pi \rightarrow \pi^*$ transition with the energy difference between the highest occupied and lowest vacant molecular orbitals (calculation by the Hückel molecular orbital method) has been demonstrated[81] for the series of sydnone imines:

$$\nu_{\pi\rightarrow\pi^*} = 23\,241 + 8366\,(m_{m+1} - m_m)\,(r = 0.938)\ .$$

On passing from non-polar to polar solvents, the long-wavelength absorption of sydnone imines, like that of sydnones, shifts towards shorter wavelengths, in full agreement with calculations[80]. Owing to the formation of hydrogen bonds, in hydroxylated solvents a pronounced hypsochromic shift of the absorption bands of $N_{(6)}$-nitrososydnone imines is observed in the visible region[73].

The $N_{(6)}$-nitrosoaminoacetonitriles, formed by the opening of the sydnone imine ring, absorb at much shorter wavelengths (approximately 230 nm for the 3-alkyl-substituted derivatives); on the basis of this difference, the kinetics of the ring opening process[82] and the reverse cyclisation reaction[51] of sydnone imine have been investigated spectrophotometrically.

A weak pale-yellow luminescence (with a maximum at approximately 510 nm) has been observed recently[82] for solid solutions of sydnone imine salts in water; a pronounced bathochromic shift of the luminescence bands relative to the corresponding absorption bands has been noted.

2. Vibrational Spectra

Characteristic intense bands due to the stretching vibrations of the exocyclic $\rangle C{=}N-$ bond (1671–1700 cm^{-1}) and deformation vibrations of the immonium group $=\overset{+}{N}H_2-$ (1588 to 1606 cm^{-1}) have been observed in the infrared spectra of sydnone imine salts[83,84]. These bands were assigned by comparing the spectra with those of the salts of iminoesters and deuterated derivatives of sydnone imines[83,84].

A low-intensity band due to the stretching vibrations of the $C_{(4)}-H$ bond has been observed in the region of 3110 to 3205 cm^{-1} in the spectra of sydnone imines unsubstituted in the 4-position[32,68]. Other systematically observed absorption bands (at 742–810 and 1160–1216 cm^{-1}) are probably associated with the deformation vibrations of the sydnone imine ring[83,84]. The positions of the characteristic frequencies depend little on the type of substituents in the 3- and 4-positions in the ring. It has been noted that the presence of a substituent at a ring carbon atom diminishes somewhat the intensity of the vibrations of the $\overset{+}{N}H_2$ group.

The band due to the stretching vibrations of the carbonyl group in $N_{(6)}$-acylsydnone imines (1620–1670 cm^{-1})[84] is displaced towards lower frequencies, compared with acyclic *N*-acylamines (1660–1680 cm^{-1}). This shift can be accounted for by the electron-donating properties of the sydnone imine ring relative to the imino-group[56]. Owing to its conjugation with the carbonyl group, the C=N bond in the $N_{(6)}$-acylsydnone imines has a stretching vibration band in the region of lower frequencies (1546–1608 cm^{-1})[56,69] than the C=N bond in the corresponding $N_{(6)}$-unsubstituted sydnone imine salts. As a result of the exclusion from conjugation of the electron pair of the exocyclic nitrogen atom, the spectra of the salts of $N_{(6)}$-acylsydnone imines[32,56,69] exhibit an appreciable shift of the carbonyl band to the $\nu(C{=}O) = 1722$–1739 cm^{-1} and of the C=N bond stretching vibration band to $\nu(C{=}N) = 1615$–1635 cm^{-1}. The study of the infrared spectra showed that in $N_{(6)}$-acylsydnone imines the proton adds to

the exocyclic nitrogen and not to the oxygen of the carbonyl group[56].

The vibration frequencies of the carbonyl groups in $N_{(6)}$-acylsydnone imines are weakly correlated with the calculated C=O bond orders[85] (the calculation was performed[86] by the Hückel molecular orbital method with parameters obtained by the PPP method).

The infrared and Raman spectra of $N_{(6)}$-carbamoylsydnone imines have been studied in detail[69] in the region of the characteristic vibrations of the $>C{=}N{-}\overset{\overset{O}{\|}}{C}{-}NHR$ group; the following assignments have been made: $\nu(C{=}O) = 1640–1660\ cm^{-1}$; $\nu(C{=}N) = 1580–1600\ cm^{-1}$; $\delta(NH) = 1510–1540\ cm^{-1}$. The bands were found[69] to have high integral intensities ($A_{C=O} = 3.1 \times 10^{4}–5.0 \times 10^{-4}$ cm^2 litre mole^{-1} and $A_{C=N} = 2.4 \times 10^{-4}–3.1 \times 10^{-4}$ cm^2 litre mole^{-1}); comparison with the spectroscopic characteristics of other $N_{(6)}$-acyl derivatives indicates an effective electronic interaction of the atoms in the group investigated. It has been shown by infrared spectroscopy[69] that the proton adds to the exocyclic nitrogen atom in the $N_{(6)}$-carbamoyl derivatives.

The value of $\nu(C{=}N)$ in the spectra of 3-hydroxysydnone imines (1680 cm^{-1}) led to the conclusion that these compounds have the zwitter-ionic (*N*-oxide) structure (IXa).[48]

Two intense bands at 1335–1355 and 1408–1421 cm^{-1}, assigned to the stretching vibrations of the N=O bond in the associated and non-associated molecules respectively, are characteristic[73] of $N_{(6)}$-nitrososydnone imines; the band at 1503–1599 cm^{-1} corresponds[73] to the exocyclic C=N bond and that at 1090–1111 cm^{-1} corresponds to the N–N bond in the $>C{=}N{-}N{=}O$ group.

The characteristic vibration frequencies of various groups attached to substituents in the 3- and 4-positions in the sydnone imine ring have been quoted in a number of investigations, namely carboxy-,[32] ester, hydroxy-, and other groups[84,87]. When the groups are close to the ring, the characteristic frequencies undergo a shift due to the electronegative properties of the mesoionic ring.

3. Nuclear Magnetic Resonance Spectra

There can be only one hydrogen atom at the carbon atom in the 4-position in the sydnone imine ring. The chemical shifts of this proton have been quoted in a number of reports as a function of the substituents at the $N_{(3)}$ and $N_{(6)}$ atoms[9,33,52,68,88]. The chemical shifts of the protons in the sydnone imine salts ($\delta = 7.4–8.1$ p.p.m.†) are located in a lower field[9,23] than for sydnones ($\delta = 6.2–6.8$ p.p.m.).[33] In $N_{(6)}$-acylsydnone imine salts the signal due to the proton at $C_{(4)}$ is displaced downfield even more ($\delta = 8.3–8.8$ p.p.m.).[52] Owing to the combination of the anisotropic effects of the two rings in the 3-aryl derivatives of sydnone imines, the signal due to the proton at $C_{(4)}$ is displaced downfield[88].

The signal due to the protons of the methyl group in 3-methyl-substituted sydnone imines is located in a very low field (5.5–5.9 p.p.m.), which indicates an appreciable positive charge on the $N_{(3)}$ atom.

† Here and henceforth the chemical shifts are relative to tetramethylsilane.

The positions of the substituents entering the molecule in electrophilic substitution (nitration and bromination) reactions involving certain $N_{(6)}$-arylcarbamolysydnone imines have been determined with the aid of the analysis of the ^{1}H NMR spectra[68].

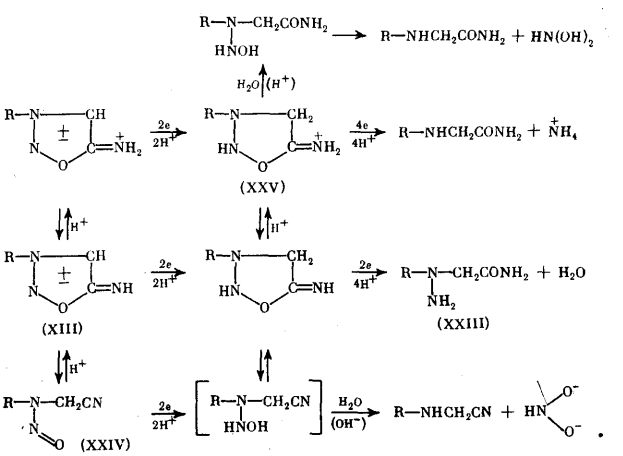
The ^{13}C NMR spectrum of 3-methylsydnone imine hydrochloride has been recently investigated and it has been shown that the $C_{(4)}$, $C_{(5)}$, and $C_{(CH_3)}$ atoms have chemical shifts of 97.3 170.4 and 40.1 p.p.m. respectively. Thus the signals due to the ring carbon atoms are located in a very high field compared with those of the carbon atoms in many other heterocycles, which in general agrees[89] with the higher effective charges on the carbon atoms in the sydnone imine ring (calculation by the CNDO/2 method).

4. Polarography

Like the sydnone ring, the sydnone imine ring is polarographically active; sydnone imine derivatives are very readily reduced at a dropping mercury electrode[27,90–98]. The influence of pH, temperature, drop period, and the addition of alcohol and the surfactants on the polarographic behaviour of sydnone imines has been investigated[90,92,94,95]. Coulometric measurements have been made to determine the number of electrons consumed at the anode[90,94,95] and it has been found that in an acid medium sydnone imine salts give rise to a single six-electron reduction wave[90,94], while in an alkaline medium $N_{(6)}$-acylsydnone imines give a four-electron wave[90,93].

Two waves are characteristic of $N_{(6)}$-acyl derivatives in the pH range 8–11: one corresponds to the reduction of the cation and the other, at more negative potentials, corresponds to the reduction of the base[92,95]. Two waves have been observed in the polarography of 3,3′-dimethylene-, trimethylene, and *p*-phenylene-3,3′-bis-sydnone imines—the reduction of the first heterocycle is facilitated under the influence of the second[98].

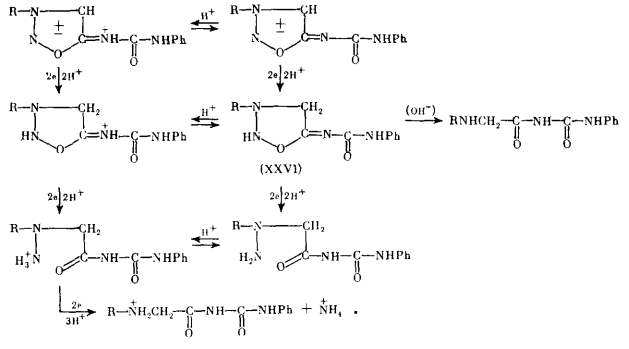
A mechanism has been proposed for the polarographic reduction of the sydnone imine cation[90]. For 3-alkyl derivatives, this mechanism has been revised[94] and can be represented schematically as follows#:



The vertical arrows in the above scheme indicate the chemical processes accompanying the reduction reactions represented horizontally.

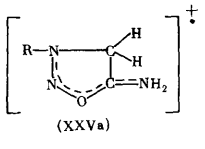
After the electrolysis of sydnone imines in a neutral medium (four electrons are consumed), the polarogram shows the anodic wave due to the oxidation of the hydrazine (XXIII); the anodic peak due to the oxidation of (XXIII) is observed likewise in cyclic voltamperometric measurements[92]. In unbuffered solutions the sydnone imine ring is partly cleaved to the *N*-nitroso-derivative (XXIV) in the region near the electrode. In the reduction of the sydnone imine ring ($c = 0.86 \times 10^{-3}$ M) in 0.1 M KCl with added 0.5×10^{-3} M HCl the splitting of the wave was observed—as a result of the increase in the alkalinity of the space near the electrode, the sydnone imine base (XIII) is formed and is involved in the production of the second wave at more negative potentials[94].

A similar mechanism has been proposed[92] for the reduction of $N_{(6)}$-carbonyl derivatives of sydnone imines and was subsequently revised and extended[95]. For example, for $N_{(6)}$-phenylcarbamoyl derivatives, it can be represented by the following scheme:



In solutions with insufficient buffer capacity it was possible to observe the reduction wave of the dihydrosydnone imine (XXVI).

The proposed mechanisms agree with quantum-chemical calculations on certain possible intermediates[96]. From the standpoint of these calculations, the capture of the first potential-determing electron followed by the addition of a proton to the $C_{(4)}$ atom with formation of the radical-cation (XXVa)



(XXVa)

is most probable. The addition of a second electron and a proton to the $N_{(2)}$ atom of this radical-cation leads to the dihydro-compound (XXV).

3-Aryl derivatives of sydnone imines have a number of characteristic features in their polarographic behaviour and their reduction mechanism is somewhat different[88].

On the basis of calculations, it has been suggested[94] that the reduction of the sydnone imine cation is greatly facilitated as a result of the gain of hydration energy on passing from the cation to the corresponding radical-cation (XXVa), which is formed following the addition of the first electron.

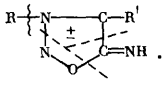
The values of $E_{1/2}$ for sydnone imines are proportional to the energies of the lowest vacant molecular orbitals calculated by the Hückel method with the parameters of Pullman and Pullman[81]. When the energies of the lowest vacant molecular orbitals calculated by the Hückel molecular orbital method are used together with the parameters obtained by the PPP method, such proportionality is observed simultaneously for sydnones and sydnone imines[86].

The validity of the Hammett and Taft equations for the sydnone imines reduction half-wave potentials $E_{1/2}$ has been demonstrated: $E_{1/2} = -0.93 + 0.37\sigma^*$ for 3-alkyl-substituted derivatives (pH 7.4);[90] $E_{1/2} = -0.63 + 0.17\sigma$ for 3-aryl-substituted derivatives[27,77] (pH 7.4);[27,93] $E_{1/2} = -0.305 \pm 0.14\sigma$ for $N_{(6)}$-methoxycarbonyl-3-aryl-substituted derivatives[27,93] (0.1 *N* HCl).

The polarographic method has been used to investigate the kinetics and equilibria in the alkaline opening of the sydnone imine ring[97,99,100]. The dynamics of the changes in the concentration of $N_{(6)}$-phenylcarbamoyl-3-phenylisopropylsydnone imine (the medicinal drug sydnocarb) in the blood of experimental animals has been followed with the aid of oscillographic polarography[101].

5. Mass Spectrometry

The most intense peak in the mass spectra of sydnone imine hydrochlorides corresponded[102] to the base (M–HCl). The heterocyclic ring of the base is cleaved preferentially into three fragments (NO, C=NH, and NCR') in accordance with the scheme



The mass spectra confirmed[48] the mode of methylation of 3-hydroxysydnone imine—both methyl groups are directed to the $N_{(6)}$ atom.

Table 1. The effective atomic charges in the sydnone imine base (XIII) and in the sydnone imine cation (II).

Method of calcn.*	Compound	$O_{(1)}$	$N_{(2)}$	$N_{(3)}$	$C_{(4)}$	$C_{(5)}$	$N_{(6)}$	Refs.
1	(XIII)	+0.242	−0.039	+0.666	−0.245	+0.068	−0.683	103
1	(II)	+0.289	+0.052	+0.653	−0.081	−0.012	+0.099	103
2	(XIII)	+0.076	−0.440	+0.536	−0.031	+0.146	−0.290	85
3	(XIII)	+0.098	−0.325	+0.476	−0.044	+0.128	−0.333	108,109
3	(II)	+0.156	−0.600	+0.531	−0.016	+0.183	+0.206	108,109
4	(XIII)	+0.157	−0.575	+0.846	−0.198	+0.125	−0.358	110
4	(II)	+0.276	−0.300	+0.847	−0.207	+0.178	+0.179	110
5	(XIII)	−0.178	−0.149	+0.234	−0.076	+0.295	−0.332	110
5	(II)	−0.063	+0.063	+0.240	−0.068	+0.346	−0.214	110

*Notation: 1) Hückel molecular orbital method, parameters of Pullman and Pullman; 2) Hückel molecular orbital method, parameters calculated by the PPP method; 3) PPP; 4) CNDO/2, π electrons (for the 3-methyl-substituted derivative); 5) CNDO/2, σ and π electrons (for the 3-methyl substituted derivative).

6. Quantum-Chemical Calculations of the Electronic Structure of Sydnone Imines

Quantum-chemical calculations on sydnone imines (and sydnones) have been carried out by various methods (see Tables 1 and 2).

The calculations were performed by the Hückel method using the parameters of Pullman and Pullman[81,103] and a self-consistent system of parameters computed from data evaluated by the PPP method[85]. The electron density distributions obtained were qualitatively independent (as regards the signs of the effective charges) of the parametrisation, but the quantitative differences between them were fairly marked. The most equalised charges were obtained using parameters calculated by the PPP method[85]. The influence of substituents in the 3-, 4-, and 5-positions has been calculated[81,85,104]. Analysis of the results shows that the sydnone imine ring (like the sydnone ring) is a weak "transmitter" of π-electronic effects from the 3-position to the 1- and 5-positions and to the exocyclic nitrogen atom and also from the 4-position to the 1- and 5-positions and from the 5-position to the 3-position; the charges on the $N_{(2)}$ and $C_{(4)}$ atoms are most sensitive to the influence of substituents in sydnone imine[85,105].

Table 2. Bond orders in the sydnone imine base (XIII) and in the sydnone imine cation (II).

Method of calcn.*	Compound	$O_{(1)}$-$N_{(2)}$	$N_{(2)}$-$N_{(3)}$	$N_{(3)}$-$C_{(4)}$	$C_{(4)}$-$C_{(5)}$	$C_{(5)}$-$O_{(1)}$	$C_{(5)}$-$N_{(6)}$	Refs.
1	(XIII)	0.411	0.752	0.498	0.670	0.373	0.576	103
1	(II)	0.447	0.758	0.485	0.786	0.408	0.312	103
2	(XIII)	0.162	0.529	0.658	0.419	0.225	0.853	85
3	(XIII)	0.212	0.532	0.609	0.485	0.240	0.821	108,109
3	(II)	0.339	0.667	0.536	0.672	0.339	0.486	108,109

*Notation: 1) Hückel molecular orbital method, parameters of Pullman and Pullman; 2) Hückel molecular orbital method, parameters calculated by the PPP method; 3) PPP.

Calculations have been made by the Hückel method on sydnone imines, sydnones, and certain other mesoionic heterocycles using the ω-technique[88,106].

The first calculation on sydnone imine in terms of the π-electron approximation by the LCAO-MO SCF method was performed[107] using a modified PPP method. Calculations have been made[108,109] on sydnone imine and sydnone by the PPP method and the influence of the initial system of parameters was analysed. In contrast to the results obtained by the simple Hückel molecular orbital method, the PPP method predicts a much higher effective charge on the $N_{(2)}$ atom than on the $C_{(4)}$ atom.

Calculations have been carried out[110] on the 3-methylsydnone imine cation and its base by the LCAO-MO SCF method in terms of the CNDO/2 valence approximation and the dipole moment of the hypothetical 3-methylsydnone imine base has been calculated ($\mu = 6.39$ *D*). A comparative calculation has been performed recently by the same method[111] on sydnone imine in which protons have been added to different atoms. Comparison of the total energies of the resulting cations showed that protonation at the exocyclic nitrogen atom is energetically most favourable. Calculations have been made in the same study[111] on certain possible intermediates in the acid cyclisation of *N*-nitrosaminoacetonitrile and the reverse reaction involving the alkaline opening of the sydnone imine ring. The calculations permitted certain hypotheses concerning the mechanisms of these reactions.

A number of studies demonstrated a fair agreement of the results of the calculations with experimental physicochemical characteristics[86,96,105,109] and the fundamental chemical properties, which will be dealt with below.

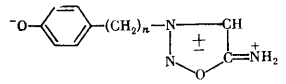
IV. CHEMICAL PROPERTIES

Like sydnone, sydnone imines are extremely reactive; reactions occurring with both retention and opening of the heterocyclic ring are characteristic of these compounds and the majority of reactions take place under fairly mild conditions.

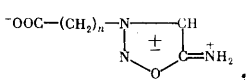
1. Reactions with Retention of the Ring

(a) *Reactions involving the exocyclic group.* The synthesis of $N_{(6)}$-exocyclic derivatives of sydnone imines, obtained by the electrophilic substitution of the hydrogen at the exocyclic nitrogen atom, was examined in detail above. These reactions take place readily and smoothly, which makes it possible to characterise the exocyclic imino-group as highly basic.

Frequent attempts to isolate the free sydnone imine bases have been unsuccessful, except for 3-hydroxy-derivatives (IX),[48] which exist as a result of betaine stabilisation. The strong base formed on neutralisation apparently undergoes autocatalytic tautomerisation to the initial nitrosoaminoacetonitrile (for further details, see below). The high basicity of the hypothetical sydnone imine base is also indicated by other facts, such as the ability to form salts with weak acids (carbonic or thiocyanic) and to form inner salts as a result of the involvement in the betaine structure of the phenolic hydroxyl of (XXVII) [9] and (XXVIII) [21] or the carboxy-group in a series of free-carboxyalkyl-substituted sydnone imines (XXIX):[32]



(XXVII) $n = 0$
(XXVIII) $n = 2$



(XXIX) $n = 1, 2$

The pK_a values have been determined for certain 3-dialkylaminosydnone imines (VI) and were found to be ~8.15–8.85,[36] i.e. are similar to, for example, the pK_a for morpholine (8.7). According to Gotz and Grozinger[36], this shows that the exocyclic nitrogen atom is protonated in these compounds, since its acylation leads to a decrease of pK_a by 4–5 orders of magnitude.

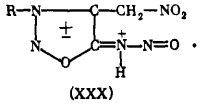
The capacity of $N_{(6)}$-acyl derivatives for protonation, which likewise confirms the high basicity of the sydnone imine "base", has been observed not only for 3-dialkylaminosydnone imines but also for compounds with hydrocarbon substituents in the 3-position[15,27,52,56]. $N_{(6)}$-Carbamoylsydnone imines possess similar properties[52]. The hydrochlorides, sulphates, and nitrates of a series of compounds of this type has been isolated in the solid state.

The basicity of $N_{(6)}$-acyl- and $N_{(6)}$-carbamoyl-sydnone imines depends significantly on the nature of the substituent in the 3- and 4-positions and in the acyl residue. The pK_a values for $N_{(6)}$-acyl derivatives vary in the range 2.5–4.6. Compounds with alkyl substituents in the 3-poisition are more basic than their aryl analogues. The substitution of the hydrogen atom at the carbon atom in the 4-position of the ring by the methyl or phenyl group leads to a decrease of capacity for salt formation.

Comparison of the pK_a values for compounds with the same exocyclic substituent, for example, the methoxycarbonyl group, reveals an increase in the basicity of the exocyclic nitrogen following the enhancement of the electron-donating properties of the substituent in the 3-position[27]. As was to be expected, in compounds with the same substituent in the 3-position, a decrease of the electronegativity of the substituent at the $N_{(6)}$ atom increases significantly the basicity for the following series of substituents: $CCl_3CO < C_6H_5CO < CH_3OCO < CH_3CO$.[56]

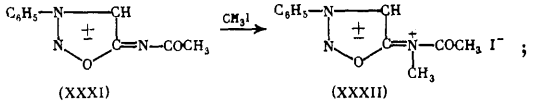
The carbamoyl analogues of $N_{(6)}$-acylsydnone imines are somewhat less basic than the latter compounds[52,101]. Benzenesulphonyl and thiocarbamoyl derivatives exhibit weak basic properties; the pK_a of the latter compounds cannot even be measured[52].

A single instance of the protonation of $N_{(6)}$-nitroso-derivatives has been described, namely of compound (XXX) having in the 4-position the nitromethyl group, which apparently stabilises the molecule[49]:

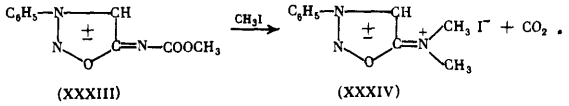


(XXX)

Evidence additional to the spectroscopic data quoted above, confirming that the protonation of $N_{(6)}$-acylsydnone imines proceeds at the exocyclic nitrogen atom, comes from the ability of these compounds to form quaternary salts[56]. Thus, when $N_{(6)}$-acetyl-3-phenylsydnone imine (XXXI) was heated with methyl iodide in acetone, the methiodide (XXXII) was obtained:



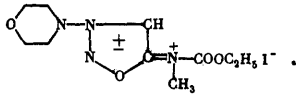
(XXXI) (XXXII)



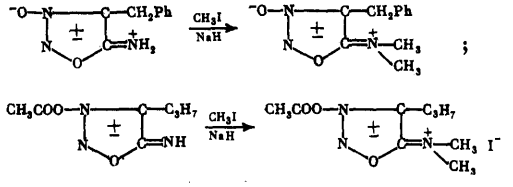
(XXXIII) (XXXIV)

Under analogous conditions, the $N_{(6)}$-methoxycarbonyl derivative (XXXIII) is converted into the quaternary salt (XXXIV).[56] Evidently the methiodide of type (XXXII) formed in the latter reaction is readily decarboxylated.

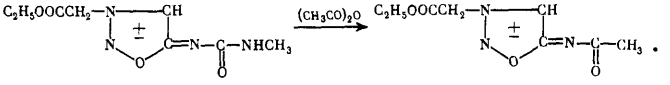
Decarboxylation was not observed in the methylation of $N_{(6)}$-ethoxycarbonyl-3-morpholinosydnone imine[59] and the final product had a structure similar to that of (XXXII):



Quaternary salts of type (XXXIV) have been obtained from 4-benzyl-3-hydroxysydnone imine and 3-acetoxy-4-propylsydnone imine by treatment with methyl iodide in the presence of sodium hydride[48]:



Other types of reactions of the exocyclic group in $N_{(6)}$-substituted sydnone imines have also been described. Thus, in the presence of boron trifluoride etherate, the $N_{(6)}$-methylcarbamoyl derivative (XXXV) is smoothly converted under the influence of acetic anhydride into the corresponding acetyl derivatives (XXXVI):[112]

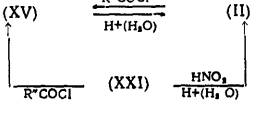


(XXXV) (XXXVI)

Certain $N_{(6)}$-acyl-3-arylsydnone imines split off the acyl group under the influence of 1 *N* HCl even at room temperature, giving rise to sydnone imine salts[41,48,52,59]. On the other hand, this reaction for the majority of other acyl derivatives requires fairly severe conditions (for example, 1 *N* HCl, 1 h, 100 °C).[52] The phenylcarbamoyl group is not eliminated under analogous conditions[52].

The acid elimination of the acyl group could be used to obtain other $N_{(6)}$-derivatives of 4-substituted sydnone imines when a sydnone imine salt cannot be used. For example, on heating the $N_{(6)}$-methoxycarbamoyl-4-bromo-3-phenylsydnone imine (XV, $R = C_6H_5$, $R' = Br$, $R'' = OCH_3$) with 2.7 *N* H_2SO_4 and subsequent nitrosation of the reaction mixture, the $N_{(6)}$-nitroso-derivative of this sydnone imine (XXI, $R = C_6H_5$, $R' = Br$) was synthesised[73].

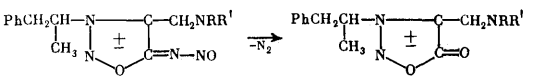
$N_{(6)}$-Nitrososydnone imines (XXI) exhibit a high reactivity. Under the influence of carboxylic acid chlorides, they are converted smoothly into the corresponding $N_{(6)}$-acylsydnone imines (XV):[25]



When the $N_{(6)}$-nitroso-derivative is treated with hydrogen chloride in alcohol, the nitroso-group is eliminated as nitrosyl chloride with formation of the sydnone imine hydrochloride[25]. This reaction also proceeds smoothly with sulphuric or hydrochloric acid, giving an almost quantitative yield. Its detailed kinetic study established[25] that the nitroso-group in compound (XXI) hydrolyses extremely readily. The reaction is catalysed by acids and proceeds via the S_N2 mechanism. Under identical conditions, $N_{(6)}$-nitrososydnone imines hydrolyse at a rate faster by several orders of magnitude than the usual *N*-nitrosoamines[25].

When $N_{(6)}$-nitroso-derivatives are heated in inert solvents, they are converted into the corresponding sydnones (I) with evolution of nitrogen[25,73]. It has been observed[25] that in alcohols and dichloroethane the reaction is slow and the yield of sydnones is frequently 25–50%; in boiling dimethylformamide (DMF) the process also proceeds partly with liberation of nitrogen oxides. On moderate heating in DMF (at approximately 90 °C), the reaction proceeds rapidly and sydnone is formed almost quantitatively[113]. This transformation is observed for compounds with aliphatic, alicyclic, and aliphatic-aromatic substituents in the 3-position and also for 4-benzylsydnone imines. The kinetic studies have led to the conclusion that the reaction is a unimolecular process, which can be classified as an S_Ni intramolecular substitution reaction.

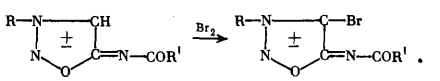
A new method of synthesising sydnones[114] can be more convenient in some cases than the usual procedure; it leads to higher yields and makes it possible to synthesise sydnones which cannot be obtained by the cyclisation of the corresponding *N*-nitrosoaminoacids. Thus the $N_{(6)}$-nitroso-derivative of 4-dimethylamino-3-phenylisopropylsydnone imine (XXXVIIa) and 3-phenylisopropyl-4-piperidinosydnone imine (XXXVIIb) are converted in almost quantitative yields into the corresponding sydnones (XXXVIIIa) and (XXXVIIIb) on heating in DMF:[49]



(XXXVII) (XXXVIII)

(a) R, $R^1 = CH_3$, (b) $RR^1 = -(CH_2)_5-$.

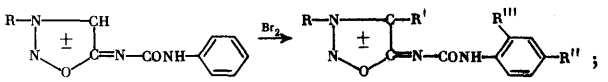
(b) Reactions involving substitution in the 4-position and transformation of side groups. By analogy with sydnones, $N_{(6)}$-acyl derivatives of sydnone imines enter into electrophilic substitution reactions involving the fourth carbon atom. Under mild conditions, the hydrogen at the $C_{(4)}$ atom is replaced by the mercuriacetate group[6]. The bromination of $N_{(6)}$-acylsydnone imines proceeds smoothly[6,9,20,42,76,115] and the reaction takes place most readily in ether in the presence of an excess of sodium bicarbonate[9,20]; the use of dibromodioxan and bromosuccinimide[20,41] leads to much lower yields:



It has been noted that substitution of 3-alkyl derivatives takes place much more readily than that of their aryl analogue[20]. Like the $N_{(6)}$-acylsydnone imines, their $N_{(6)}$-sulphonyl derivatives undergo the bromination reaction[75].

On bromination of $N_{(6)}$-carbamoylsydnone imines containing alkyl substituents in the exocyclic group, substitution by bromine, as in the $N_{(6)}$-acyl analogues, takes place at the $C_{(4)}$ atom of the sydnone imine ring[68].

In the course of the bromination of $N_{(6)}$-phenylcarbamoyl-3-butylsydnone imine (XXXIX, $R = C_4H_9$), it was observed[41] that bromine enters the benzene ring and not the sydnone imine ring and it was postulated that this leads to the formation of the *p*-bromo-derivative (XL, $R = C_4H_9$):



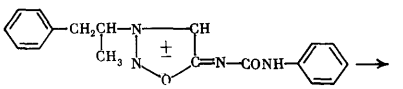
(XXXIX) (XL): $R^1 = R''' = H$, $R'' = Br$;
(XLI): $R''' = H$, $R^1 = R'' = Br$;
(XLII): $R^1 = R'' = R''' = Br$.

A detailed study of the bromination of $N_{(6)}$-phenylcarbamoylsydnone imines showed[68] that, when equimolar amounts of bromine are used, *p*-bromophenyl derivatives (XL) are indeed formed. An increase of the amount of bromine to 2 moles leads to the substitution of both the benzene and sydnone imine rings in (XLI). When the reaction was carried out in the presence of a large excess of bromine, the tribromo-derivative (XLII) was obtained.

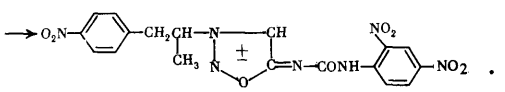
The introduction of chlorine and iodine atoms into the 4-position of $N_{(6)}$-acyl-3-morpholinylsydnone imines with the aid of chloro- and iodo-succinimide has been described[41,115].

The attempt to substitute at the $C_{(4)}$ atom by treatment with chlorine or sulphuryl chloride led only to the cleavage of the sydnone imine ring[116]. In contrast to sydnones, the bromine in $N_{(6)}$-acyl-4-bromosydnone imines could not be substituted by lithium[75].

Nitration of $N_{(6)}$-phenylcarbamoyl-3-arylalkylsydnone imines with a mixture of nitric and acetic acid at room temperature gives rise, in contrast to sydnones, to the corresponding nitrate salts only[68]. Under more severe conditions (treatment with a mixture of nitric and sulphuric acid), $N_{(6)}$-phenylcarbamoyl-3-phenylisopropylsydnone imine (XLIII) is converted into a trinitro-derivative, to which structure (XLIV) was attributed:

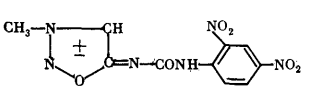


(XLIII)

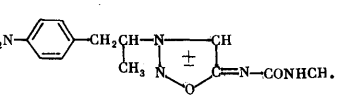


(XLIV)

$N_{(6)}$-Phenylcarbamoyl-3-methyl- and $N_{(6)}$-methylcarbamoyl-3-phenylisopropyl-sydnone imines give rise under these conditions, to the nitro-derivatives (XLV) and (XLVI) respectively without a nitro-group in the sydnone imine ring:



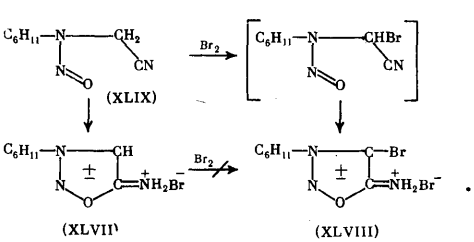
(XLV)



(XLVI)

In the bromination and nitration reactions a decrease of the nucleophilic activity of the $C_{(4)}$ atom of the sydnone imine ring is observed relative to the phenylcarbamoyl group.

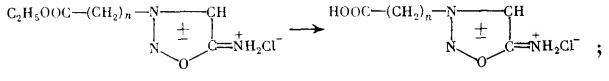
The impossibility of introducing the nitro-group into the sydnone imine ring is apparently due to the sharp decrease of the nucleophilic activity of the entire molecule and in the first place of the carbon atom in a strongly acid medium owing to the protonation of the exocyclic nitrogen atom. For the same reason, it is impossible to brominate 3-cyclohexylsydnone imine hydrobromide (XLVII) by treatment with bromine in chloroform[20]. The expected product (XLVIII) was obtained by allowing a solution of *N*-nitroso-*N*-cyclohexylaminoacetonitrile (XLIX) in bromine-containing methylene chloride to stand for a long time, whereupon compound (XLVII) was isolated together with compound (XLVIII). Apparently there is initially substitution of the hydrogen at the α-carbon atom by bromine, which results in the evolution of hydrogen bromide, under the influence of which both nitrosonitriles cyclise;



(XLIX) (XLVII) (XLVIII)

Thus exocyclic derivatives of sydnone imines can enter into electrophilic substitution reactions involving a ring carbon atom, provided that the formation of the cationic form of the molecule is excluded during the process.

Apart from the examples of the involvement of the side groups of sydnone imines in bromination and nitration reaction quoted above, a number of other instances are also known were side groups react, while the mesoionic ring remains unaffected. Thus 3-carboxymethylsydnone imine hydrochloride (La), which could not be obtained by direct synthesis, has been prepared by the hydrolysis of the corresponding ethyl ester (LIa) (which is available) with hydrochloric acid at room temperature[64]:



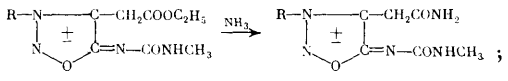
(LI) (L)

(a) $n = 1$.

The hydrochlorides of other carboxylalkylsydnone imines (L) [33] have been synthesised analogously and the esters of $N_{(6)}$-carbamoyl and $N_{(6)}$-thiocarbamoyl-3-carboxymethylsydnone imines have been converted into the corresponding acids[64].

Under the influence of aqueous ammonia at room temperature, the ester group in the 3- or 4-positions in $N_{(6)}$-methylcarbamoylsydnone imines is smoothly converted into the amide group[58,117].

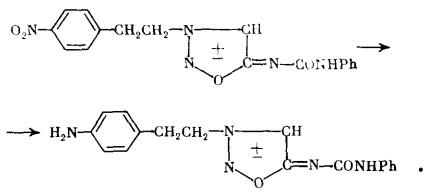
In contrast to the compound with the methyl substituent in the 3-position (LIIa), its phenyl analogue (LIIb) undergoes ring cleavage with further rearrangement under these conditions, in addition to the formation of the amide:



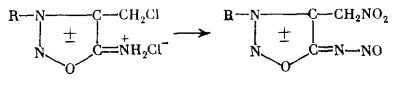
(LII)

(a) R = CH_3, (b) R = Ph.

By virtue of the considerable stability of the $N_{(6)}$-carbamoyl derivatives, it was possible to reduce the nitro-group in the benzene ring of the substituent with the aid of iron in acetic acid[68]:



Interesting reactions are observed for 4-chloromethylsydnone imines (LIII).[49] On treatment with sodium nitrite in water or methanol, a reaction involving both the exocyclic group and the side chain takes place. The reaction products were found to be $N_{(6)}$-nitroso-derivatives of 4-nitromethylsydnone imines (LIV):

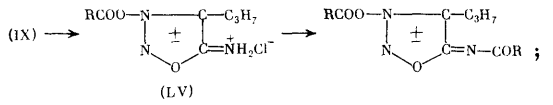


(LIII) (LIV)

This indicates a high mobility of the chlorine atom in the chloromethyl group.

Incidentally, attempts to obtain 4-chloro- or 4-bromomethyl derivatives of sydnone imines by substituting the hydrogen atom by a halogen in *N*-acyl-4-methylsydnone imines under various conditions were unsuccessful[49].

The simultaneous involvement in the reaction of the exocyclic nitrogen atom and the side chain was observed also in the acetylation or carbamoylation of 3-hydroxy-4-propylsydnone imine[33] (IX). In the first place the reaction involves the oxygen atom, as shown by the formation of the monosubstituted product (LV):



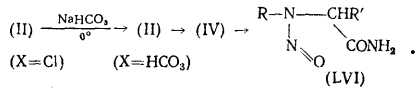
(LV)

R = CH_3, or NHPh.

2. Reactions with Opening of the Ring

The high reactivity of sydnone imines is manifested particularly strikingly in reactions leading to the opening of the heterocyclic ring. Ring cleavage can take place at different bonds under the influence of various reagents.

(*a*) *The action of alkalis and bases.* When sydnone imine hydrochlorides are treated cautiously with sodium bicarbonate at 0 °C, it is possible to isolate acid carbonate salts, but even at room temperature the ring opens under these conditions with formation of the initial *N*-nitrosoaminonitrile[9]:

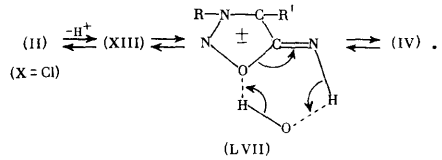


(LVI)

When sydnone imine salts are treated with a solution of sodium carbonate or caustic alkalis and also on being passed through an anion-exchanger, saturated with hydroxide ions, the reaction products are the corresponding *N*-nitrosoaminoacetamides (LVI), probably obtained as a result of the hydrolysis of the nitriles produced initially[7,9,97,118].

The formation of *N*-nitrosoacetamide has been observed also on treating sydnone imine hydrochloride with piperidine[119]. It has been shown by a polarographic procedure for a series of 3-alkylsydnone imine hydrochlorides[99] that they are rapidly converted in a weakly alkaline medium (pH 11) into *N*-nitrosoaminoacetonitriles (IV), which give rise to the corresponding amides (LVI) at higher pH values.

The kinetics of the alkaline opening of the ring in 3-isopropylsydnone imine hydrochloride has been studied spectrophotometrically[120] and it has been established that the process is reversible in the pH range 7.15–8.60 and is of first order with respect to the sydnone imine and of second order with respect to hydroxide ions. The authors[120] suggest that the first stage involves the elimination of a proton from the salt, leading to the formation of the base (XIII), which is a cyclic tautomer of the final cleavage product—*N*-nitrosoaminoacetonitrile (IV). The rate-limiting stage of the process is a bimolecular reaction involving the attack on the base (XIII) by a hydroxide ion. The resulting reaction complex, which may have the bicyclic structure (LVII), is converted into (IV) either directly with elimination of a hydroxyl or via an intermediate:

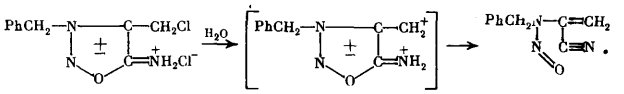


(LVII)

It has been observed that in the case of 3-arylsydnone imines the reaction is of first order with respect to both the heterocycle and the hydroxide ion[97]. Apparently here too

the first stage involves the elimination of a proton from the sydnone imine cation with formation of a base, which undergoes spontaneous ring opening to give compound (IV) without the involvement of the OH^- ion or an activated complex. This difference in the mechanism can probably be accounted for by the conjugation between the sydnone imine and benzene rings in the 3-arylsydnone imine base.

In the series of 3-arylalkylsydnone imines there is also a possibility of ring opening not catalysed by hydroxide ions. Thus, it has been noted that the hydrochloride of 3-benzyl-4-chloromethylsydnone imine (LIIIa, $R = C_6H_5CH_2$) undergoes ring cleavage even under the influence of water[49]. α-(*N*-Nitrosobenzylamino)acrylonitrile (LVIII) was isolated as the final product:



(LIIIa) (LIX) (LVIII)

The process probably involves the initial elimination of a chloride ion from the chloromethyl group with formation of the unstable dication (LIX), which is stabilised with elimination of two protons and the opening of the ring to give the unsaturated nitrile (LVIII).

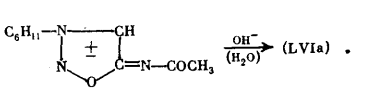
The determination of the rate and equilibrium constants made it possible to elucidate the effect of substituents on the stability of the sydnone imine ring in an alkaline medium[90,107]. Electron-donating substituents in the 3- and 4-positions, which lower the electrophilic activity of the entire molecule and of the reaction centre in relation to the reaction catalysed by hydroxide ions, increase the stability of the ring. It has been shown recently[121] that even the carboxy-group in 3-carboxyalkylsydnone imines promotes an increase of the stability of the ring compared with the 3-methyl derivative.

A detailed study of the alkaline opening of the ring in the hydrochloride of 3-morpholinosydnone imine[122] showed that this process has the general characteristic observed for sydnone imines with hydrocarbon substituents in the 3-position.

All the available data permit the conclusion that the opening of the ring in sydnone imine salts is not a result of hydrolysis but constitutes a tautomeric ring–chain reversible transformation: sydnone imine base ⇋ *N*-nitrosoaminoacetonitrile.

N-Exocyclic derivatives of sydnone imines are much more stable in relation to alkalis and bases, like sydnones[46].

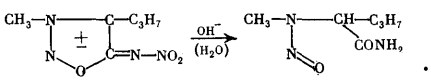
While the majority of $N_{(6)}$-acylsydnone imines are resistant to the action of alkalis at room temperature, they are cleaved on raising the temperature. Thus heating of $N_{(6)}$-acetyl-3-cyclohexylsydnone imiine for 10 min with a 10% solution of sodium hydroxide gives an almost quantitative yield of *N*-cyclohexyl-*N*-nitrosoaminoacetamide (LVIa):[52]



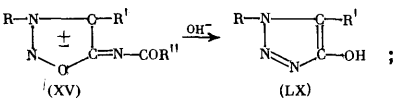
(LVIa).

It has been shown in relation to $N_{(6)}$-ethoxycarbonyl-3-morpholinosydnone imine[122] that the first stage of the alkaline cleavage of $N_{(6)}$-acylsydnone imines involves the formation of the "base", as for sydnone imine salts, which is subsequently converted into a nitrosonitrile and a nitrosoamide.

$N_{(6)}$-Nitro-derivatives undergo an alkaline decomposition analogously for $N_{(6)}$-acylsydnone imines[7]:



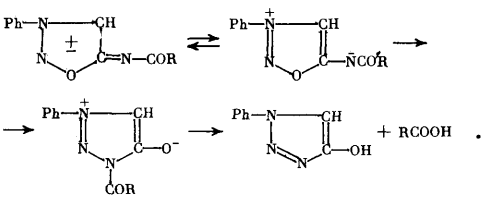
When $N_{(6)}$-acylsydnone imines are treated with a methanol solution of potassium hydroxide, the formation of *N*-nitrosoaminoacetamides, which are obtained also in an aqueous medium, can be accompanied by other reactions[52]. Thus $N_{(6)}$-acyl-3-butyl- and $N_{(6)}$-acyl-3-phenyl-sydnone imines (XV, a and b) give rise to the corresponding nitrosoamides (LVI) even at room temperature. In the latter case the main reaction product proved to be 4-hydroxy-3-phenyl-1,2,3-triazole (LXb), which is obtained with a high yield on heating (XVb) with a 10% potassium hydroxide solution in methanol:



(XV) (LX)

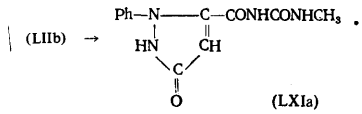
(a) $R = C_4H_9$, $R' = H$, $R'' = CH_3$, C_2H_2Ph;
(b) $R = Ph$, $R' = H$, $R'' = CH_3$, C_2H_5, or Ph;
(c) $R = R' = Ph$, $R'' = C_2H_5$.

The reaction involving $N_{(6)}$-propionyl-3,4-diphenylsydnone imine (XVc) also proceeds analogously. It is believed[52] that under these conditions ring opening is accompanied by a rearrangement which can be represented by the following scheme:



$N_{(6)}$-Carbamoylsydnone imines are more resistant to alkalis than the corresponding acyl derivatives, but, on heating with an alcoholic solution of potassium hydroxide, their heterocyclic ring is opened[52]. Urea derivatives were isolated among the cleavage products.

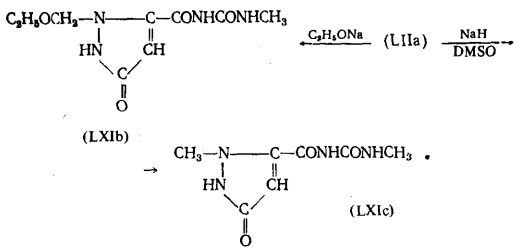
It was mentioned above[117] that, in contrast to the 3-methyl analogue, $N_{(6)}$-methylcarbamoyl-4-ethoxycarbonylmethyl-3-phenylsydnone imine (LIIb) undergoes preferential cleavage on treatment with aqueous ammonia at room temperature, forming a rearrangement product—5-pyrazolinone (LXIa):



(LXIa)

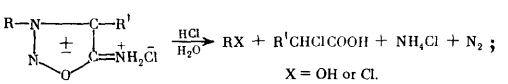
Derivatives of 5-pyrazolinone (LXI, b and c) have been isolated and identified after treating $N_{(6)}$-methylcarbamoyl-4-ethoxycarbonylmethyl-3-methylsydnone imine (LXIIa) with

sodium ethoxide[117] or hydride[123]:



These reactions apparently involve the simultaneous or successive rupture of the $N_{(2)}-O_{(1)}$ bond in the ring and the intramolecular acylation of the unsubstituted nitrogen atom by the carboxymethyl group.

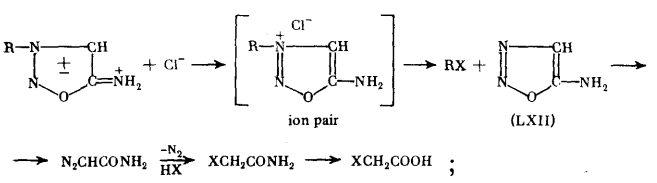
(*b*) *The action of acids*. It was believed initially that, in contrast to sydnones, sydnone imine salts are resistant to the action of acids even on raising the temperature[6,11]. However, a detailed study showed that, on heating with hydrochloric acid, sydnone imines are cleaved with liberation of nitrogen and formation of the corresponding halogeno- or hydroxy-derivatives, substituted chloroacetic acids, and ammonium chlorides[9,123,125]:



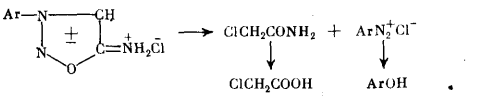
The study of the kinetics of the cleavage of sydnone imine hydrochlorides with aryl substituents in the 3-position showed[125,126] that nitrogen is evolved via a first-order reaction and that the pseudo-unimolecular rate constant is directly proportional to the HCl concentration but is independent of that of H_2SO_4. This confirms that the reaction is catalysed by chloride ions and not protons.

The rate of hydrolysis of sydnone imine salts increases with enhancement of the electron-donating properties of the substituents or with increase of their bulk[125,127]. It has been suggested[125] that the acid hydrolysis of 3-alkylsydnone imine salts is an S_N1 reaction, the first rate-limiting stage of which involves dissociation of the $R-N_{(3)}$ bond with formation of the carbonium ion R^+ and the unstable 5-amino-1,2,3-oxadiazole molecule (LXII). The latter decomposes with evolution of nitrogen and the formation of the amide of glycolic acid. In hydrochloric acid the hydroxy-group is replaced by chlorine and the amide group is converted into a carboxy-group. The R^+ cation reacts instantaneously with water to form the alcohol ROH, while in the presence of chloride ions the chloride RCl is formed.

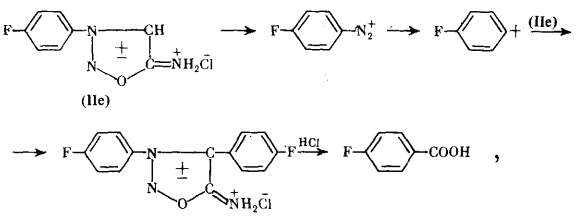
The specific effect of HCl can apparently be explained by the ability of the sydnone imine cation to form ion pairs with Cl^-:



Another mechanism of the acid cleavage has been established for 3-arylsydnone imines[128]. In this case an arenediazonium chloride and chloroacetamide are formed and are subsequently converted into phenol and chloroacetic acid:

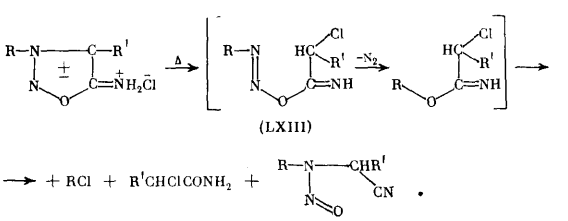


Direct confirmation of the intermediate formation of an arenediazonium compound in this reaction has been obtained[119] by employing the hydrochloride of 3-(4′-fluorophenyl)sydnone imine (IIe). *p*-Fluorobenzoic acid, whose formation has been explained[120] by the mechanism



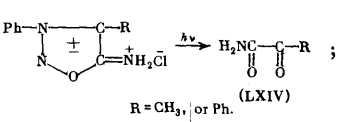
was then detected in the reaction mass.

(*c*) *Thermal and photochemical cleavage*. Sydnone imine salts with non-aryl substituents have been found to undergo thermal as well as hydrolytic cleavage, the former beginning to predominate at high chloride ion concentrations[125,127]. A detailed study of this process led to the hypothesis that in the given instance, when the concentration of the ion pair is high, the first reaction stage involves the dissociation of the $N_{(3)}-C_{(4)}$ bond with formation of the unstable diazoiminoester (LXIII), which is subsequently converted into the corresponding alkyl chloride and amide via the iminoester[125,127]:

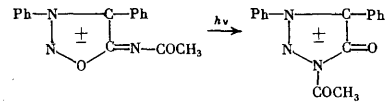


The thermal cleavage of the sydnone imine ring can occur on heating sydnone imine salts in non-aqueous solvents, for example in DMF and in butyl alcohol[127]. Together with the products formed on thermal decomposition of the salts in water, the corresponding *N*-nitrosoaminoacetonitrile is obtained. An exception is 3-benzyl derivative, from which benzyl chloride is apparently initially split off, as in an aqueous medium, while 5-amino-1,2,3-oxadiazole (LXII) is cleaved further with participation of yet another sydnone imine molecule to give the final products[128].

Examples of the photochemical cleavage of the sydnone imine ring have been described. Thus, on irradiation of aqueous solutions of the hydrochlorides of 4-methyl-3-phenyl- and 3,4-diphenyl-sydnone imines with light from a mercury lamp for 20–40 h, the corresponding dicarbonyl compounds (LXIV) are formed in 8–9% yield[129]:



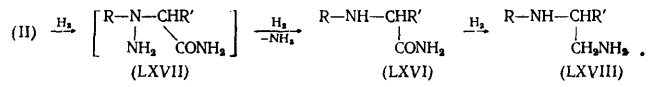
Morpholine, glycolic acid, and nitrogen were identified among the products of the photochemical decomposition of the hydrochloride of 3-morpholinosydnone imine[122]. After ultraviolet irradiation of $N_{(6)}$-acetyl-3,4-diphenylsydnone imine, it was possible to detect the mesoionic triazolone (LXV) among the decomposition products[130]:



(LXV)

Morpholine, chloroacetic acid, ethyl alcohol, and carbon dioxide were found among the products of the photolysis of $N_{(6)}$-ethoxycarbonyl-3-morpholinosydnone imine in 0.1 *N* HCl solution[122].

(d) Other ring cleavage reactions. The sydnone imine ring is opened also in catalytic hydrogenation. In an early study Brookes and Walker[7] observed that, when the hydrochlorides of 4-isopropyl-3-methyl- and 4-isobutyl-3-methylsydnone imines are reduced over a platinum catalyst, the corresponding aminoacetamides (LXVI) are formed and ammonia is evolved;

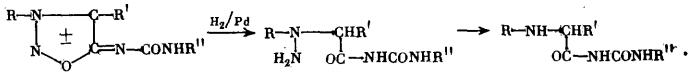


(LXVII) (LXVI) (LXVIII)

Since in the reduction of a sydnone imine salt over a palladium catalyst the first two moles of hydrogen are absorbed rapidly, the authors[9] suggested that a hydrazinoamide (LXVII) is formed initially and is then deaminated on further reduction to give (LXVI). They showed that, in the reaction of the hydrochloride of 3,4-diphenylsydnone imine (IIb), the formation of an amide of type (LXVI) is accompanied under these conditions by the formation of a product of further hydrogenation—*N*,*C*-diphenylethylenediamine.

It was mentioned above that, when $N_{(6)}$-phenylcarbamoylsydnone imines are reduced with iron, ring cleavage is not observed[68], but hydrogenation over palladium black leads to ring opening in these compounds[52].

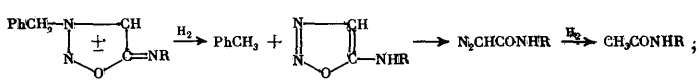
The main product of the reductive cleavage of $N_{(6)}$-carbamoylsydnone imines is the hydrazine derivative (LXIX):



(LXIX) (LXX)

In an acid medium or on hydrogenation of the hydrochlorides of $N_{(6)}$-carbamoyl derivatives, the deamination product (LXX) is formed preferentially.

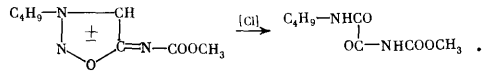
As in thermal cleavage, hydrogenolysis of sydnone imines with a benzyl substituent in the 3-position (LXXI) takes place differently. It has been shown[131] that under these conditions the primary step is debenzylation with successive formation of unstable oxadiazoles (LXXII) and acetyldiazoacetamides (LXXIII). The latter can be partly hydrogenated to the corresponding acetamides:



(LXXI) (LXXII) (LXXIII)

R = H · HCl, $COCH_3$ or CONHPh.

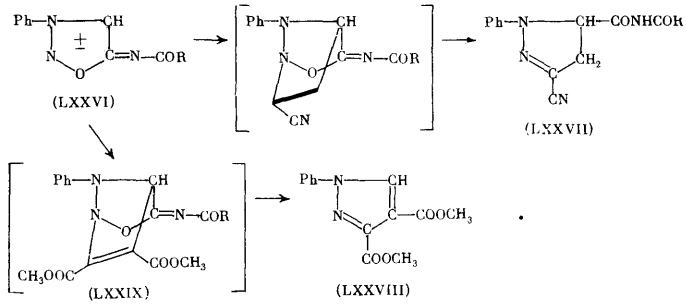
Yet another example of the oxidative cleavage of the sydnone imine ring has been described[116]. In contrast to sydnones, which are chlorinated fairly smoothly in the 4-position in the ring, when sydnone imine salts were acted upon by chlorine their decomposition was observed and the individual products could not be isolated. On treatment of $N_{(6)}$-methoxycarbonyl-3-butylsydnone imine (LXXIV) with chlorine in dichloroethane in the presence of sodium dicarbonate or with sulphuryl chloride in dichloroethane and subsequent treatment of the reaction mixture with water, the cleavage product was isolated to which the structure (LXXV) was attributed:



(LXXIV) (LXXV)

Like sydnones, $N_{(6)}$-acylsydnone imines enter into 1,3-dipolar addition reactions with unsaturated compounds[132]. Thus, when $N_{(6)}$-methoxycarbonyl- and $N_{(6)}$-benzoyl derivatives of 3-phenylsydnone imines (LXXXVI, a and b) are heated with an excess of acrylonitrile, the sydnone imine ring is opened with formation of a new ring (the pyrazoline ring). In contrast to sydnones, the ring oxygen and the exocyclic group are not then eliminated and the final reaction product is a derivative of 1-phenylpyrazoline-5-carboxylic acid (LXXVII, a and b), i.e. 1,3-addition with a subsequent rearrangement takes place.

On the other hand, the reaction with dimethyl acetylenedicarboxylate proceeds via a "sydnone" type mechanism[133]: on prolonged heating with $N_{(6)}$-benzoyl-3-phenylsydnone imine (LXXVIb), the main reaction products isolated were dimethyl 1-phenylpyrazole-3,4-dicarboxylate (LXXVIII) and dibenzoylurea:



(LXXVI) (LXXVII) (LXXIX) (LXXVIII)

The authors[133] suggest that the latter is formed as a result of the elimination of benzoyl isocyanate from the intermediate (LXXIX), analogous to the elimination of CO_2 when the similar reaction is carried out with sydnones.

3. Characteristics of the Reactivity of Sydnone Imines

It follows from the examination of the chemical behaviour of sydnone imines that these compounds exhibit a high and many-faceted reactivity due to a number of their structural features, primarily the unusual distribution of electron density in the unsaturated heterocyclic system, including the exocyclic group.

The relative reactivities of sydnone imines are on the whole consistent with the calculations of the distribution of electron density. The ease of their hydrolytic and thermal decomposition is consistent with the presence of a large positive charge on the $N_{(3)}$ atom in sydnone imine salts. The enhanced electron density at the exocyclic nitrogen atom in

$N_{(6)}$-acyl and $N_{(6)}$-carbamoyl derivatives is confirmed by the high basicity of these compounds. The excess electron density at the $C_{(4)}$ atom in $N_{(6)}$-acylsydnone imines determines the mode of the electrophilic substitution reaction. The large negative charge on the exocyclic nitrogen atom in the sydnone imine base is consistent with the ease of the electrophilic substitution at and addition to this atom. As already mentioned above, calculations indicate a fair agreement with the values of $E_{1/2}$ for the polarographic reduction of sydnone imines[81,86].

Quantitative analysis of the reactivity of sydnone imines with the aid of equations based on the principle of the linearity of free energies (LFE), namely in terms of the influence of substituents on the kinetics and equilibria in certain reactions, made it possible to deduce the properties of the sydnone imine ring as a transmitter of the electronic effects of both the reaction centre and the substituent[58,87,97,99,100].

Substituents in the 3-position exhibit an inductive effect in relation to reactions involving the exocyclic group and the influence of these substituents is correlated satisfactorily with the Taft inductive constants (σ^*) of non-aryl substituents and the σ^0 constants of aryl substituents.

In view of the identical order of magnitude of the constants σ^* and σ^0 ($\sigma^* = 0.600 + \sigma^0$), the data for 3-substituted derivatives can be combined into a single reaction series. Thus a single straight line has been obtained for the basicities of $N_{(6)}$-methoxycarbonyl-3(R)-sydnone imines[100]:

$$pK_a = 3.50 - 0.65\,\sigma^* \quad (r = 0.990),$$

and two virtually parallel straight lines have been obtained for the kinetics of the acid hydrolysis of the nitroso-group in $N_{(6)}$-nitroso-3(R)-sydnone imines[87,135]:

$$\lg k = -3.84 + 0.39\,\sigma^* \quad \text{(for non-aromatic R)},$$
$$\lg k = -4.06 + 0.39\,\sigma^* \quad \text{(for aromatic R)}.$$

The distance between these straight lines along the ordinate axis ($\psi = -0.22$) is determined by the non-polar conjugation of the exocyclic N=O group with the benzene ring in the 3-position; the calculated energy of this conjugation is low[87,135]: $E_\psi = 2.3RT\psi = 0.3$ kcal.

Reactions involving the exocyclic group are also satisfactorily correlated with the σ^0 constants of 4-aryl substituents, as shown in the conversion of $N_{(6)}$-nitroso-4-aryl-3-benzylsydnone imines into the corresponding sydnones ($\rho^0 = 0.18$) and in the acid hydrolysis ($\rho^0 = 0.24$) and polarographic reduction of the nitroso-group ($\rho^0 = 0.025$) in these compounds[87].

The sydnone imine ring is a reaction centre in polarographic reduction[90,93]; the correlation analysis of the half-wave potentials $E_{1/2}$ in accordance with the LFE principle has already been described. For the alkaline opening of the sydnone imine ring[82,97,100], which in this case also behaves as a reaction centre, the equilibrium constant for derivatives with non-aromatic substituents in the 3-position is described satisfactorily by the equation[99,100]

$$\lg K = -6.63 + 2.44\sigma^* + 0.46E_S^c, \qquad (1)$$

where E_S^c is the steric constant of the substituents. The steric hindrance in the ring opening reaction can apparently be accounted for by the "expansion" of the substituents at the $N_{(3)}$ atom on passing from the sp^2 hybridisation of this atom in the sydnone imine to the p^3 state in *N*-nitrosoaminoacetonitrile. The equilibrium constant for this reaction involving 3-(R)-aryl derivatives is described by the equation[27,99,100]

$$\lg K = -6.16 + 2.44\,\sigma^0. \qquad (2)$$

Comparison of Eqns.(1) and (2), taking into account the fact that $\sigma^* = 0.600 + \sigma^0$ and $E_S^c \cong 0.25$ for R = aryl, led to the calculation[99,100] of the effect of the non-polar conjugation of the benzene and sydnone imine rings ($\psi = -1.2$) and of the energy of this conjugation: $E_\psi = 1.6$ kcal. The energy of the non-polar conjugation with the sydnone imine ring for the phenyl substituent in the 4-position is[87] $E_\psi \cong -2.0$ kcal. These values of E_ψ are smaller by a factor of approximately four than the energy of the conjugation of the two benzene rings in biphenyl.

The following equations have been obtained for the kinetics of the alkaline ring opening (pH 8.75):

$$\lg k = -2.374 + 1.00\,\sigma^0 \quad (3(R) = Ar)^{27,100},$$
$$\lg k = -3.19 + 1.86\,\sigma^* \quad (3(R) = Alk)^{91}.$$

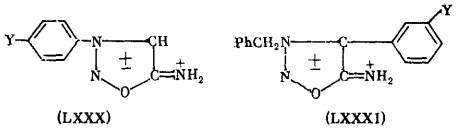
The absence of a steric effect in the latter case can serve as evidence in support of the view that the activated complex in this reaction has a geometry closer to that of the initial sydnone imine than that of *N*-nitrosoaminoacetonitrile[97]. On the other hand, as stated above, a considerqble "steric acceleration" effect was observed in the acid cyclisation reaction[51].

The rate-limiting stage in the thermal cleavage of the hydrochlorides of 3-alkyl- and 3-aryl-sydnone imines (except 3-benzylsydnone imine) involves the interaction of the chloride ion with the $C_{(4)}$ atom and subsequent rupture of the $N_{(3)}-C_{(4)}$ bond. The substituent at $N_{(3)}$ is in the *ortho*-position with respect to the ring $C_{(4)}$ atom and therefore exhibits a considerable steric as well as electronic effect[127]:

$$\lg k = -3.21 + 0.90\sigma^* + 1.00E_S^c \text{ (DMF, 89°)}.$$

The retardation of the reaction as the bulk of the substituent increases and its electron-donating capacity is diminished supports an S_N2 mechanism for this reaction, since a steric acceleration of the reaction might have been expected for an S_N1 mechanism[127].

The Hammett constants σ for the sydnone imine ring have been calculated from the half-wave potentials $E_{1/2}$ for the polarographic reduction of the Y group in compounds of the type (LXXX) and (LXXXI):[98]



(LXXX) (LXXXI)

The results are presented below; the σ constants of the sydnone ring and of the *N*-nitrosoaminoacetonitrile group, from which sydnone imine groups are synthesised, are included for comparison:

Substituent	σ
p-(3-sydnone iminyl)	+1.1
m-(3-benzyl-4-sydnone iminyl)	+0.40
p-[N(N=O)CH$_2$CN]	+0.5
p-(3-sydnonyl)	+1.0
p-(3-benzyl-4-sydnonyl)	+0.3

The values of σ indicate strong electron-accepting properties of the 3-sydnone iminyl substituent; the addition of a heterocycle to the 4-position entails an appreciable weakening of these properties. Sydnones and sydnone imine cations proved to have similiar σ constants, while the opening of the sydnone imine ring leads to a decrease of the electronegativity by a factor greater than two.

V. BIOLOGICAL PROPERTIES OF SYDNONE IMINES

Like sydnones, sydnone imines are not found in nature and have no analogues among the known natural and synthetic biologically active substances. However, the high and varied reactivity of sydnone imines as well as the possibility of converting them under mild conditions into *N*-nitroso-compounds and aminoacid derivatives led investigators to study their biological activity. Data have now been obtained on the antibacterial, antitumour, pharmacological, and biological activities of a number of sydnone imine derivatives[88,135]. By analogy with sulphonamide preparations, incorporating a five-membered nitrogen-containing heterocycle with an exocyclic amino-group (ethazole, norsulphazole, etc.), a study was made of the antimicrobial activity of $N_{(6)}$-*p*-aminobenzenesulphonyl derivatives of sydnone imines (XIX, $R'' = NH_2$).[10,72] However, like the hydrochlorides of 4-alkyl-3-methylsydnone imines[7], these compounds proved to be relatively inactive in relation to various experimental infections. Among 3-piperonylsydnone imines, substances with antimalarial activity were discovered[26].

The antiblastic activity of a number of mono- and bis-sydnone imines has been investigated on small laboratory animals[8,136]. Among the lower alkyl derivatives, compounds with antitumour activity were not discovered[8]. On the other hand, it has been shown that[136] 3-isopropyl-, 3-cyclohexyl-, 3-piperidinylethyl-, and a number of alkylene-bis-sydnone imines are able to inhibit at least one of the five grafted tumours employed. The dichloride of ethylenebis-3,3'-sydnone imine [V, $Z = (CH_2)_2$] and its $N_{(6)}$-bismethoxycarbonyl derivative proved to be the most active in relation to sarcoma 45 and M-1 in rats and sarcoma 180 in mice. In one of the experiments 80% inhibition of the growth of sarcoma 45 was noted. It has been observed that in the general case the salt form of sydnone imines has a favourable influence on the antiblastic activity and that, with increase of the length of the hydrocarbon chain in polymethylenebis-3-sydnone imines, the antiblastic activity falls. It has been suggested that the antitumour activity of sydnone imines is associated with their conversion into *N*-nitrosoaminoacid derivatives, some of which have an inhibiting effect on tumour growth.

Interesting results have been obtained in the study of the pharmacological activity of sydnone imine derivatives. As a result of extensive research by Soviet and Japanese scientists, substances which have found applications as medicinal drugs have been found among compounds of this series. It has been discovered that many salts of 3-aryl-,[9] 3-benzyl-,[16] and 3-ethoxycarbonylmethyl-sydnone imines[17] as well as their $N_{(6)}$-acyl[53-55,57] and $N_{(6)}$-carbamoyl[53-55,58,64,65,74,112] derivatives exhibit analgesic and antipyretic activities. Together with the analgesic and antipyretic activities, certain hydrochlorides of 3-arylsydnone imines show an anti-inflammatory action[17,64,65,74,112]. It has been stated[53-55] that certain 3-aryl- and 3-benzyl-sydnone imines can be used in the treatment of rheumatism.

It has been found[137] that, among the series of sydnone imine salts with hydrocarbon substituents investigated, only the 3,4-diaryl derivative shows a spasmolytic activity. An analogous activity is also exhibited by certain 3-amino-sydnone imines[45].

Pharmacological studies have shown that many sydnone imine salts and their exocyclic derivatives exhibit a hypotensive activity. A fairly prolonged effect has been observed for compounds containing the benzyl group in the 3-position[16]. In experiments on cats the hydrochloride of 3-phenoxyethyl-sydnone imine reduced the arterial pressure by 30–50 mm for 1–2 h.[13] The hydrochlorides of 3-cyclobutyl- and 3-cyclopentyl-sydnone imines have been patented as vasodilators[49]. Sydnone imine salts containing 4-benzyl, 4-*o*-methoxyphenyl-, 4-piperonyl-, and 4-α-pyridylpiperazinoalkyl substituents in the 3-position show antianginal and hypotensive activities.

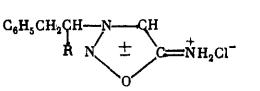
However the hypotensive activity is exhibited most strikingly by 3-amino-derivatives[138]. In small doses, the hydrochlorides of 3-dimethylamino-,[37,38,44] 3-dibutylamino-,[37,45] 3-piperidino-,[37,38,43,45] 3-(α-pipecolinyl)-,[38,43,45] 3-pyrrolidino-,[37,38,43,45] 3-morpholino-,[37,38,43,45,118,139,140] and 3-(4'-methylpiperazino)-sydnone imines[38,45] reduce blood pressure for a long time.

The salts of 3-aminosydnone imines containing in the 4-position chlorine or bromine atoms[41,42,45] or alkyl substituents[43] as well as the dihydrochloride of 3,3'-(1'',4''-piperazino)bis-sydnone imine[37,38,45] have a dilating effect on the coronary artery. The $N_{(6)}$-acyl derivatives of 3-aminosydnone imines containing the benzoyl[44,61], cyclohexanecarbonyl[44,115], and ethoxycarbonyl[62,63] residues at the exocyclic nitrogen atom proved to be still more effective.

From compounds of this type, Japanese investigators selected one substance—$N_{(6)}$-ethoxycarbonyl-3-morpholinosydnone imine—which was subjected to an extensive pharmacological study[141-143]. Under the names SIN-10, morsydomine, or morial[144], this sydnone imine has found application as a hypotensive drug. The use of a specimen labelled at the $C_{(5)}$ atom[145] made it possible to investigate in detail the pharmacokinetics and metabolism of this preparation[146]. It has been suggested[143] that the mechanism of its hypotensive action based on its ability to block α-adrenergic receptors.

In the series of sydnone imines substances acting on the central and peripheral nervous systems have been discovered: these are the salts of certain 3-aminosydnone imines[39] and their $N_{(6)}$-acyl derivatives[60] as well as various 3-phenylalkylsydnone imines[12,13,21,147]. It has been shown that the salts of a number of sydnone imines exhibit an adrenopositive peripheral activity and exert a stimulating influence on the central nervous system[12,147]. The inhibiting effect of these compounds on the enzyme monoamine oxidase has been studied in detail[12,33,147]. It has been shown the sydnone imine salts inhibit the oxidative deamination of a number of biogenic amines and that the majority of the compounds cause reversible competitive inhibition of enzymes. Among a whole series of the sydnone imine salts investigated with different substituents in the 3- and 4-positions, the most effective inhibitors in relation to tyramine and serotonine as substrates *in vitro* proved to be the hydrochlorides of 3-phenylethylsydnone imine (LXXXII) and 3-phenylisopropylsydnone imine (LXXXIII), whose activity [$I_{50} = (1.8–6.6) \times 10^{-5}$ M] is comparable to that of iproniazid. An increase of the bulk of the group in the 3-position [$(C_6H_5)_2CHCH_2$ and $(C_6H_5CH_2)_2CH$] and the replacement of hydrogen in the 4-position by the CH_3 or C_6H_5 group lowers the inhibiting effect[12,148].

The hydrochloride of 3-phenylisopropylsydnone imine showed a high activity also in *in vivo* experiments on rats and it was demonstrated that the inhibiting effect is exhibited by the sydnone imine itself and not by products of its metabolism:



(LXXXII), R = H
(LXXXIII), R = CH_3

The results of biochemical studies permitted a specific investigation of the pharmacological activities of the compounds which enhance the activity of biogenic amines[12,147]. It was found that the intensity of pharmacological effects in this series of compounds is more notable the higher the ability of the sydnone imine salts to inhibit the oxidation of biogenic imines, which serve in the organism as chemical mediators in nervous excitation.

Among alkyl- and aryl-sydnone imines, substances were discovered which influence the central nervous system and exhibit a peripheral sympathomimetic activity[147-149]. They diminish somewhat the sedative and hypothermal activity of reserpine, enhance the convulsant effect of tryptamine and 5-hydroxytryptophan, and intensify the motor activity of animals. Among them, the highest pharmacological activity was shown by the hydrochloride of 3-phenylisopropylsydnone imine (LXXXIII), which under the name sydnophen has found applications in psychiatric practice as a medicinal drug acting both as a psychostimulator and antidepressant[22,23,24,150-153].

An interesting pharmacological activity is manifested by $N_{(6)}$-phenylcarbamoyl-3-phenylazopropylsydnone imine (XLIII), which is an effective psychostimulator. In experiments on animals this compound increases motor activity, shortens the latent period in conditioned reflexes, has an activating effect on the bioelectric processes in the cortex and subcortical structures of the brain, weakens the effect of hypnotic substances, and increases the body temperature. This relatively non-toxic substances has found applications as a medicinal drug (under the name sydnocarb) stimulating the central nervous system in the treatment of various mental illnesses and in other cases, and it has many advantages over other preparations with similar activities[67,154-160]. A similar study of the pharmacokinetics of sydnocarb by chromatographic[161] and polarographic[101] methods and a procedure using synthetic [^{14}C]sydnocarb specimens labelled in different sites within the molecule[162] made it possible to establish clearly the characteristics of the action of this preparation, its metabolism, its distribution in the organism[163], and its elimination from the latter.

During the preparation of the manuscript for the press, several reports on the chemistry of sydnone imines were published. It has been shown[163] that the sydnone imine ring can be formed not only under the conditions of acid catalysis but also under the conditions of base catalysis; the intermediate cyclisation product, formerly regarded as the hypothetical base of the sydnone imine (XIII), has been detected spectroscopically.

Infrared spectroscopic data have led to the conclusion that the side chain in $N_{(6)}$-carbamoylsydnone imines has a planar structure and an inference has been drawn about its conformation[164]. A number of $N_{(6)}$-aminoalkylacyl derivatives of sydnone imines have been synthesised by the method of polymeric activated esters[165].

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