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CATION RADICALS OF N-SUBSTITUTED PHENOTHIAZINES

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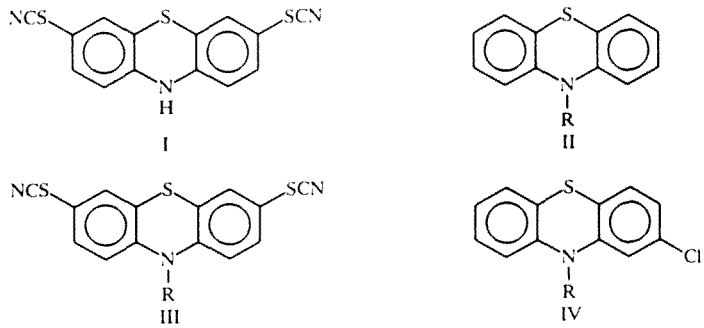
The reaction of N-substituted phenothiazines with certain acceptors (halogenated solvents $CHCl_3$, CH_2Br_2, CCl_4, o-chloranil, $AlCl_3$, $SnCl_4$, concentrated H_2SO_4, concentrated HNO_3 in $HClO_4$) has been studied by EPR spectroscopy. The hyperfine structure in the EPR spectra of the cation radicals is analyzed. To interpret the EPR spectra obtained in terms of the MNDO-PM3 method we carried out a calculation of the electronic structure of phenothiazine cation radicals containing $N-CH_3$ and $N-CH_2R$ substituents. In these radical systems, there are significant steric hindrances to conformational rotation of the CH_2 substituent around the $N-C$ bond leading to a conformation with magnetically non-equivalent protons in the methylene group.

We have previously synthesized and investigated the physico-chemical properties of a series of phenothiazines I-IVa, b [1-3]. In particular, we studied their tendency to one electron oxidation in the presence of certain electron acceptors (o-



I — IV a R = CH_3, b $CH_2C{\equiv}CH$

chloranil, o-bromanil, conc. H_2SO_4, and conc. HNO_3 in $HClO_4$ medium). The cation radicals formed have been studied by the EPR method and by magnetic susceptibility and their thermal stability investigated. The EPR spectra, using each of the indicated oxidants with the N-methyl derivatives II-IVa, consist of a sextet in the ratio 1:4:7:7:4:1 pointing to an almost equal interaction of the unshared electron with the nitrogen nucleus and the three equivalent protons of the CH_3 groups ($a_N = a_H$ = 7.5-8.0 Oe) (Fig. 1). This confirms that there is free rotation of the methyl group about the $N-CH_3$ bond and is in agreement with literature data [5, 6]. At the same time, the EPR spectrum of the cation radicals having a $CH_2C{\equiv}CH$ substituent on nitrogen are a quartet with the approximate intensity ratio 1:2:2:1. This is unexpected in view of the interaction of the unshared electron with the nitrogen nucleus and two equivalent methylene group protons. These facts do not lend themselves to an unambiguous interpretation.

With the aim of a detailed study of the properties of phenothiazines and their cation radicals having CH_2R and CHR_2 substituents on nitrogen, we have synthesized the following compounds

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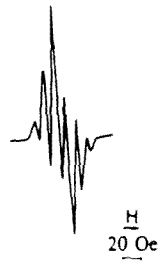


Fig. 1. EPR spectrum of Va Vd in CCl_4.

Fig. 2. EPR spectrum of treated with $SnCl_4$.

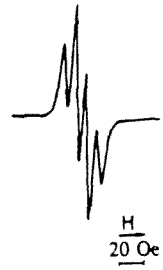


Fig. 3. EPR spectrum of Vc in benzene treated with o-chloranil.

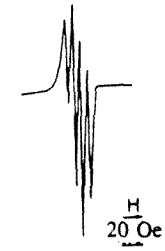
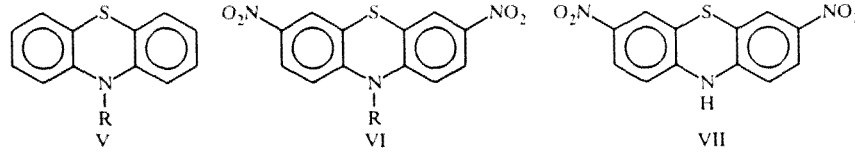


Fig. 4. EPR spectrum of Ve in conc. H_2SO_4.



V — VIIa R = CH_3, b $CH_2C{\equiv}CH$, c CH_2CH_3, d $CH_2C_6H_5$, e $CH(CH_3)_2$

Introduction of nitro groups at positions 3 and 7 of the phenothiazine ring leads to narrower lines in the EPR spectra due to the absence of splitting by the benzene ring protons and lends increased stability of the phenothiazine towards oxidation by light and atmospheric oxygen. Some parameters of these phenothiazines are given in Table 1.

We have broadened the class of oxidant used. Along with acid reagents (conc. H_2SO_4, conc. HNO_3 in $HClO_4$), we have used $AlCl_3$, $SnCl_4$, o-chloranil, and o-bromanil, as well as CCl_4, $CHCl_3$, and CH_2Br_2. The potential of the last three halogenated solvents to oxidize phenothiazines to form cation radicals has been demonstrated by us in [4].

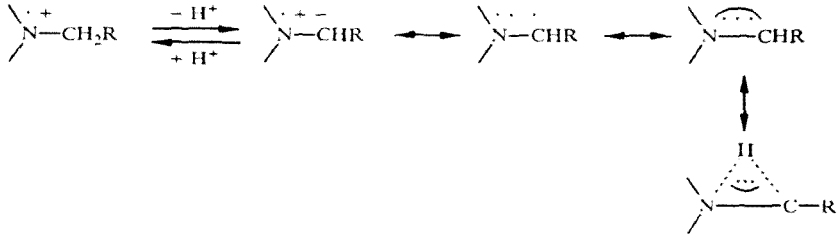
The EPR spectra, obtained by treating phenothiazines V-VIb-e containing the $N-CH_2R$ and $N-CHR_2$ substituents with the above oxidants, were similar and appeared as a quartet (1:2:2:1) (Figs. 2-4). In a number of publications there are reports of a similar pattern of hyperfine structure in the EPR spectra of phenothiazine cation radicals containing a methylene group on the nitrogen atom. Hence, in [7], a similar quartet was seen for N-ethylphenothiazine cation radicals obtained by the action of conc. H_2SO_4 on N-ethylphenothiazine. The authors rationalized this in terms of protonation of the nitrogen atom in acid medium and the resulting absence of splitting by the methylene proton. However, this hypothesis cannot be applied to cases where the oxidants are non-acidic reagents like o-quinones or CCl_4. Nor is there found experimental evidence for the proposal that fission of the substituent occurs from the nitrogen atom [8].

A further hypothesis explaining the anomalous behavior of the current EPR spectra considers that cation radicals containing the $N-CH_2R$ and $N-CHR_2$ substituents can act as n-acids to form radicals with three electrons along two atoms (e.g., as shown in Scheme 1 below).

TABLE 1. Parameters for V-VII

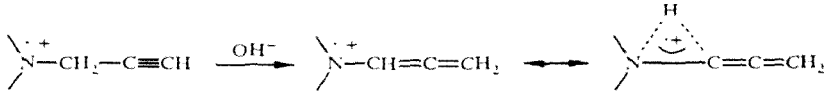
Compound	R	Empirical formula	mp, °C	IR spectrum, cm^{-1}	Yield, %
Va	CH_3	$C_{13}H_{11}NS$	100...101	2970 (ν_{as} CH_3), 1470 (δ_{as} CH_3), 1370 (δ_s CH_3), 1620 (ring vibration)	94
Vb	$CH_2—C\equiv CH$	$C_{15}H_{11}NS$	85...86	3270 (ν≡C—H), 1610 (ring vibration)	20
Vc	CH_2CH_3	$C_{14}H_{13}NS$	103...104	2930 (ν $CH_{aliph.}$), 1480 (δ $CH_{алиф}$), 1370 (δ $CH_{aliph.}$), 1620 (ring vibration)	58
Vd	$CH_2C_6H_5$	$C_{19}H_{16}NS$	82...86	2940 (ν $CH_{aliph.}$), 1370 (δ $CH_{aliph.}$), 1480 (δ $CH_{aliph.}$), 1610 (ring vibration)	48
Ve	$CH(CH_3)_2$	$C_{15}H_{15}NS$	107...109	1330, 1470 (δ CH_3), 1620 (ring vibration)	80
VIa	CH_3	$C_{13}H_9N_3O_4S$	218...220	1510 (ν_{as} NO_2), 1360 (ν_{as} NO_2), 1370 (shoulder) (δ_s CH_3), 1480 (δ_{as} NO_2), 1620 (ring vibration)	88
VIb	$CH_2—C\equiv CH$	$C_{15}H_9N_3O_4S$	139...140	1510 (ν_{as} NO_2), 1365 (ν_s NO_2), 3270 (ν≡C—H), 1480 (δ $CH_{aliph.}$), 1620 (ring vibration)	61
VIc	CH_2CH_3	$C_{14}H_{11}N_3O_4S$	214...216	1510 (ν_{as} NO_2), 1360 (ν_s NO_2), 1370 shoulder (δ $CH_{aliph.}$), 2930 (ν CH_{aliph}), 1480 (shoulder) (δ $CH_{aliph.}$), 1620 (ring vibration)	79
VIe	$CH(CH_3)_2$	$C_{15}H_{13}N_3O_4S$	210...211	1520 (ν_{as} NO_2), 1360 (ν_s NO_2), 1330, 1470 (δ $CH_{aliph.}$), 2930 (ν $CH_{aliph.}$), 620 (ring vibration)	63
VII	H	$C_{12}H_7N_3O_4S$	286...287	1510 (ν_{as} NO_2), 1365 (ν_s NO_2), 3370 (ν NH)	60

Scheme 1



The existence of such an unusual bridged structure (Scheme 1) might explain the actual hyperfine splitting in the EPR spectra of the cation radicals obtained on oxidation of V-VIIa-e. In the case of the N-isopropyl derivative, the bridged cation radical shown in Fig. 5 may also exist. Evidently, the equilibrium for the deprotonation reaction can be shifted to the right under certain conditions (e.g., in basic medium or using basic reagents) where the oxidation of V-VIIb can be accompanied by acetylene–allene rearrangement and subsequent formation of the bridged cation radical (Scheme 2).

Scheme 2



However, it is difficult to suppose that a similar scheme might be appropriate to strongly acid media, e.g., in concentrated H_2SO_4 or HNO_3.

In order to resolve this question and to interpret the EPR spectra of phenothiazine cation radicals with an N-methylene group, we have carried out a calculation of the electronic structure of the cation radicals of N-methyl, N-ethyl, N-allyl, and N-propargyl phenothiazines. These calculations were carried out using the MNDO-PM3 method [10] with optimization of all structural parameters.

The results, corresponding to an optimum potential energy surface (Figs. 6a-d), showed that the phenothiazine fragment is planar with structural parameters changing little with the substituent on the nitrogen atom. However, the structural geometries

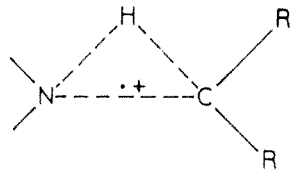


Fig. 5. Structure of the bridged N-isopropylphenothiazine cation radical.

of these substituents relative to the phenothiazine were different. In contrast to the N-ethyl, N-allyl-, and N-propargyl cation radicals, in which the N–C bond lies virtually in the phenothiazine ring plane (SNC angles of 176.6, 175.2, and 175.0°), the N-methyl analog has an angle between the N–C bond and phenothiazine ring plane of 153.2°. This significant structural difference leads to various possibilities for conformational rotation of the substituent around the N–C bond.

For the other discussed substituents of the type $-CH_2R$ and $-CHR_2$, the situation is rather different. As seen in Figs. 6b-d, the distance between the methylene group hydrogens and the hydrogen atoms at positions 1 and 9 of the phenothiazine ring are decreased when compared with the methyl group. They are 1.747 Å for $-CH_2CH_3$, 1.743 Å for $-CH_2CH{=}CH_2$, and 1.760 Å for $-CH_2C{\equiv}CH$ (this value is given for optimization in terms of the geometric energy). With conformational rotation of the substituent about the N–C bond, the given distance can be reduced even further, leading to significant steric hindrance.

Hence, the analysis of the structural parameters of these phenothiazine cation radicals shows that a significant steric interaction hinders the conformational rotation of the CH_2R and CHR_2 substituents around the N–C bond. The rather large values of the energy gradient for the structural parameters in the minima found (corresponding to the unshielded conformation relative to the C–C bond on the potential energy surface) can point to the possible existence of other extremes relating to other hindered conformations. This indicates that, for the CH_2R and CHR_2 substituents, there can be structural conformations with magnetically non equivalent methylene group protons. As a result there can be a broadening of the middle components in the EPR spectra, thus giving a quartet with the approximate intensity ratio 1:2:2:1. This proposal for hindered conformations has been supported by attempts [5] to interpret the four-component EPR spectra (1:2:2:1) of phenothiazine cation radical with an $N-CH_2CHMeNHMe_2$ substituent and also [8] in the analysis of the EPR spectra of certain cation radicals of N-substituted phenothiazine cation radicals containing the $N-CH_2R$ fragment.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument for Vaseline oils and KBr tablets. EPR spectra were taken on an EPA-2M instrument for evacuated ampuls using Mn^{2+} ions in an MgO lattice as standard. The concentration of the solutions for EPR was in the range $2\text{-}5\cdot10^{-3}$ molar (benzene, acetonitrile).

3,7-Dinitrophenothiazine (VII). Sodium nitrite (5 g, 0.072 mole) was added to a mixture of phenothiazine (5 g, 0.017 mole) in chloroform (20 ml) and acetic acid (5 ml) and the mixture was stirred for 1 h, more CH_3COOH added (5 ml), and stirring was continued for a further 15 min. The progress of the reaction was monitored chromatographically on Silufol UV-254 plates, eluting with a mixture of petroleum ether and ethyl acetate (4:1 by volume) and visualization in UV light. At the completion of the reaction, the brown precipitate was filtered and washed with glacial acetic acid, alcohol, water, and again alcohol. The product was crystallized from aniline to give VII (60%) with mp 286-287°C.

3,7-Dinitro-N-propargylphenothiazine (VIb). To a solution of VII (1.5 g, 0.005 mole) in benzene (50 ml) there were added DMSO (0.9 ml), aqueous NaOH solution (50%, 1 ml), and tetraethylbenzylammonium chloride on the end of a spatula. A mixture of propargyl bromide (0.7 ml, 0.008 mole) and DMSO (0.8 ml) at 37-39°C was added with stirring to the obtained mixture. Stirring was continued for 6 h. The reaction was monitored on the same TLC plates using benzene and ethyl acetate (4:1) eluent and visualization in UV light. At the end of the reaction, water (1:1) was added and the separated organic layer washed with water to neutrality. Drying over sodium sulfate and removal of solvent gave red-brown crystals (61%) with mp 139°C (alcohol).

N-Propargylphenothiazine (Vb) was synthesized by a known method [1].

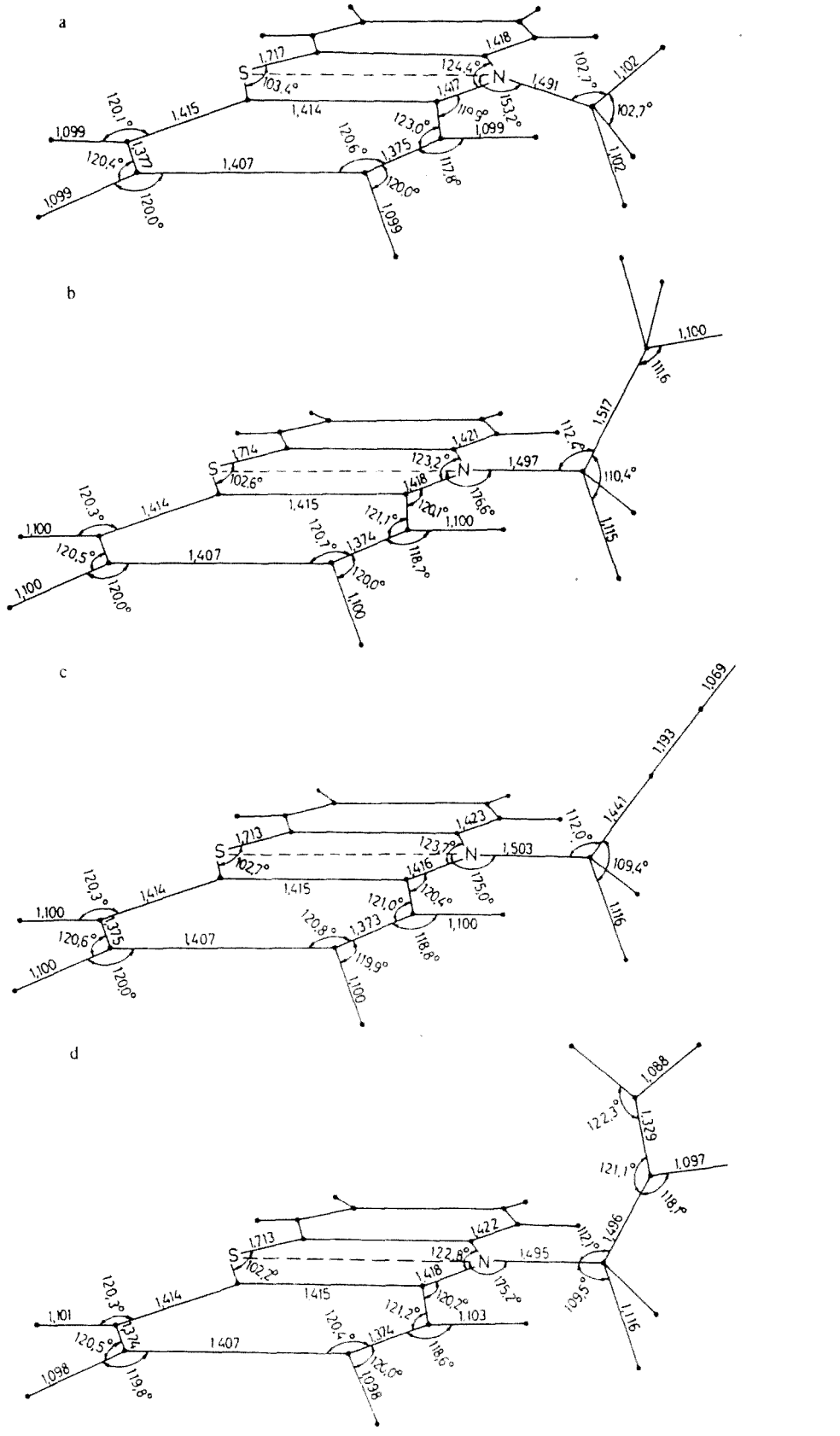


Fig. 6. a) Structural parameters for cation radical of phenothiazine VIa; b-d) structural parameters for the cation radicals of the phenothiazines: b = VIc, c = VId, d = cation radical of N-allylphenothiazine.

N-Methylphenothiazine (Va). Phenothiazine (2 g, 0.01 mole) was heated with methyl iodide (0.93 ml, 0.015 mole) for 30 h at 120°C in an evacuated ampul. The mixture was left at room temperature for 12 h, the solvent removed, and the product crystallized from alcohol to give Va (94%) with mp 100-101°C.

Vc, Vd, Ve, VIa, VIc, VId were obtained similarly.

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