TABLE 4. Intensity of the Peaks of Characteristic Ions of the 2-Chloro-5-aryl-1,3,4-thiadiazoles in the Complete Ion Current (% $\Sigma_{45}$)

| Compound | $M^+$ | $F_7$ | $F_8$ | $F_9$ | $F_{10}$ | $F_{11}$ |
|---|---|---|---|---|---|---|
| X | 24,6 | 5,1 | 5,7 | 1,9 | 5,9 | 3,0 |
| XI | 16,6 | 3,8 | 15,5 | 1,5 | 4,9 | 3,2 |
| XII | 15,6 | 7,0 | 11,9 | 2,2 | 2,2 | 4,1 |
| XIII | 20,4 | 8,8 | 7,2 | 2,4 | 2,0 | 3,7 |
| XIV | 23,1 | 11,5 | 10,3 | 3,3 | 0,6 | 2,1 |

B. To the solution of 1.1 g (5 mmoles) of the thiadiazole (II) in 120 ml of concentrated HCl at −10°C is added 0.85 g of sodium nitrite in 6.5 ml of water; the mixture is stirred for 2 h. The mixture is heated to 70°C; it is cooled, and the residue is filtered off. The substances obtained by the methods A and B are identical according to the melting points, the TLC, and the mass spectra.

The compounds (XI)-(XIV) were obtained by the method A.

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# 10-ALKENYLPHENOTHIAZINES.

## 2.* SYNTHESIS AND MECHANISM OF ACIDIC HYDROLYSIS OF cis- AND trans-10-2-PHENYLVINYL)PHENOTHIAZINES


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UDC 547.869.2:542.938:541.634



The addition of phenothiazine to phenylacetylene in super-base media proceeds regio- and stereoselectively and leads to the predominant formation of cis-10-(2-phenylvinyl)phenothiazine, which is completely converted to its trans-isomer at 200°C. Kinetic analysis of the acidic hydrolysis of the cis- and trans-isomers has allowed us to assign to it an $AS_E2$ reaction mechanism, similar to the mechanism of hydrolysis of vinyl alkyl ethers.


The reaction of phenothiazine with acetylene is used for the preparation of 10-vinylphenothiazine (I) [2, 3]. The reaction of phenothiazine with acetylene homologs has not been described in the literature, although it is obvious that these reactions would represent a straightforward method for the synthesis of a wide variety of 10-alkenylphenothiazines. In

*For Communication No. 1, see [1].


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Translated from Khimiya Geterotsicheskikh Soedinenii, No. 10, pp. 1420-1424, October, 1986. Original article submitted June 26, 1985.

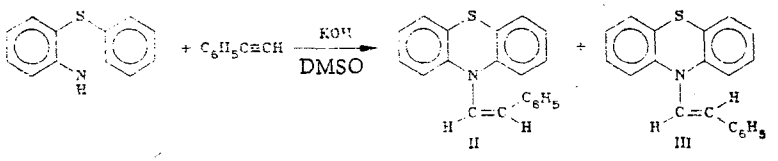
TABLE 1. cis-10-(2-Phenylvinyl)phenothiazine (II) and trans-10-(2-Phenylvinyl)phenothiazine (III)

| Compound | mp [bp (hPa)] | IR spectrum, $cm^{-1}$ | UV spectrum, $\lambda_{max}$, nm (log ε), in hexane | PMR spectrum, δ, ppm | | Found, % | | | | Molecular formula | Calculated, % | | | | Synthesis conditions | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | $H_A$ | $H_B$ (J, Hz) | C | H | N | S | | C | H | N | S | T, °C | time, h | |
| II | 140—141 | 1640, 915 | 256 (4,63), 303 (3,89), 333 sh (3,76) | 6,5 | 6,3 (8,5) | 79,6 | 5,1 | 4,6 | 10,3 | $C_{20}H_{15}NS$ | 79,7 | 5,0 | 4,7 | 10,6 | 100<br>150 | 2<br>12 | 56<br>44 |
| III | 169—170 [245 (6,65)] | 1650, 920 | 258 (4,48), 308 (4,35), 333 sh (4,24) | — | 6,3 (14,5) | 79,6 | 5,4 | 4,7 | 10,4 | $C_{20}H_{15}NS$ | 79,7 | 5,0 | 4,7 | 10,6 | 100<br>150 | 2<br>12 | 17<br>47 |

TABLE 2. Kinetic and Activation Parameters for the Hydrolysis of Compounds II and III [II, III = $(2.0-2.8)\cdot10^{-3}$ M; HCl = $(0.97-9.30)\cdot10^{-4}$ M; 60% aqueous dioxane]

| Compound | T, °C | k, liter/mole·sec | $E_A$, kJ/mole | $\Delta H^{\neq}$, kJ/mole | $\Delta S^{\neq}$, J/K·mole | KIE $= k_H/k_D$ |
|---|---|---|---|---|---|---|
| II | 60 | 0,30±0,01 | 76,5±5,1 | 73,6±5,1 | −34,9±0,7 | 3,6±0.3 |
| | 68 | 0,59±0,02 | | | | |
| | 76 | 0,95±0,03 | | | | |
| | 83 | 1,89±0,08 | | | | |
| III | 60 | 0,81±0,02 | 57,5±3,0 | 54,7±3,1 | −83,8±0,3 | 3,1±0,2 |
| | 64 | 0,96±0,06 | | | | |
| | 68 | 1,30±0,03 | | | | |
| | 76 | 2,05±0,05 | | | | |

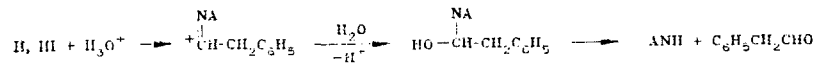
super-base media, namely, KOH in DMSO [4], phenothiazine has been found to react with phenylacetylene, to give the cis- and trans-isomers of 10-(2-phenylvinyl)phenothiazine (II and III) in quantitative yield under mild conditions (relative to acetylene).




The reaction proceeds quantitatively (according to TLC) and at a significant rate at temperatures of 100°C and higher. The ratio of isomers II/III is determined primarily by the reaction temperature, and the yield of the trans-isomer III increases as the temperature is raised (see Table 1). We have also shown by independent experiments that compound II can be quantitatively converted to its trans-isomer III in the absence of solvent within 4 h at 200°C. The observed results are consistent with a kinetically controlled reaction of phenothiazine with phenylacetylene to give the cis-isomer II, which isomerizes under the reaction conditions to the thermodynamically more stable trans-isomer III. The results for this reaction are in contrast to the results obtained by us earlier for the reaction of phenylacetylene with carbazole and indole [5], in which the main products were found to be the cis-isomers of 9-(2-phenylvinyl)carbazole and 1-(2-phenylvinyl)indole, respectively; the trans-isomers were not formed at all under these reaction conditions.

The lower thermodynamic stability of the cis-isomer II compared to the trans-isomer III is probably associated with three-dimensional steric interactions of the cis-phenyl group and the phenothiazine ring in compound II which would be expected to reduce the overall conjugation of the system due to deviations of the phenothiazine and phenyl groups from the plane of the C=C bond. This conclusion is also substantiated by the UV spectra of compounds II and III. As can be seen in Table 1, the trans-isomer III exhibits a bathochromic shift and increased conjugation of molecule III compared to its cis-isomer II.

It has previously been demonstrated that in electrophilic addition reactions to the C=C bond, and also, in part, in the acidic hydrolysis of phenothiazine (I), attack of the electrophile occurs exclusively at $C_\beta$ [6], but that, on the other hand, acidic hydration of styrene involves in addition protonation of the terminal vinyl atom [7]. Based on these results, it could be assumed that catalytic acidic hydration of compounds II and III could proceed by two pathways, with intermediate formation of either a carbenium-immonium ion or a benzyl cation. In fact, hydrolysis of either II or III in dioxane–water in the presence of hydrochloric acid has been found by TLC to give complete decomposition of II or III to phenothiazine and phenylacetaldehyde; no other products were detected. These results allow us to conclude that the p-π conjugation effect predominates over the resonance effect of the phenyl group. It should also be mentioned that the cis-isomer II is significantly more susceptible to hydrolysis than the corresponding cis-isomer of 9-(2-phenylvinyl)carbazole (IV) (see [5]).

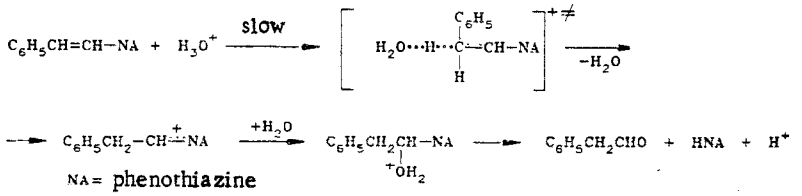



NA = phenothiazine

It has also been established previously by spectral methods [5], that in compound IV the p-π conjugation effect is inhibited by steric interaction of the planar carbazole fragment and the cis-phenyl group, which decreases the electronic density at the β-vinyl carbon atom and also reduces its reactivity relative to 9-vinylcarbazole (V). It is anticipated that there would be less steric inhibition of the p-π conjugation effect in molecule II compared to compound (IV) due to the nonplanar structure of the phenothiazine ring [8, 9].

We have studied the kinetics of acidic hydrolysis of compounds II and III in aqueous dioxane (40:60%) in the presence of hydrochloric acid. The reaction order for the hydrolysis of compounds II and III was unitary with respect to both catalyst and substrate, and the reaction followed the Arrhenius equation within the temperature range 60-83°C. Table 2 gives the second order rate constants for the hydrolysis of compounds II and III at various temperatures, as well as the activation energies, and the enthalpies and entropies of activation, as calculated based on the Eyring equation. The kinetic isotope effect of the reaction medium was determined by measuring the rate of hydrolysis of compound II or III in a mixture of dioxane and $D_2O$ in a 60:40% ratio in the presence of CDl as catalysttat 60°C. It was found that the hydrolysis rate was slower in $D_2O$; $k_H/k_D = 3.6 \pm 0.3$ for the cis-isomer II and $3.1 \pm 0.2$ for the trans-isomer III.

The negative entropy of activation value (Table 2) corresponds to a bimolecular mechanism [10]; this observation leads us to the assumption that the transition state involves transfer of a proton from the catalyst to the substrate. The reduced rate of hydrolysis in $D_2O$ is consistent with this assumption, namely, that the slow step involves proton transfer to the β-vinyl carbon atom in compound II or III. In the case of the hydrolysis of 9-vinylcarbazole under similar conditions, the values of the entropy of activation and KIE are $-20.0 \pm 0.2$ eu and $3.1 \pm 0.3$ [11], respectively. In the case of phenothiazine I, the kinetic isotope effect due to the reaction medium for hydrolysis in aqueous dimethoxyethane solution was 3.3 [6]. In the same study it was demonstrated that, depending on the solvent composition, $\Delta S^{\neq}$ for compound I varied between 18 and −14 eu. The $\Delta S^{\neq}$ and isotope effect values thus reveal that a similar hydrolysis mechanism is in effect for compounds II and III, 9-alkenylcarbazoles [11], compound I [6], and simple vinyl ethers; in the case of the latter compounds, $k_H/k_D$ is in the range 2.5-3.3 [12, 13]. Hydrolysis of compounds II and III proceeds according to the following scheme ($AS_E2$ mechanism).




It should be mentioned that both the trans- and cis-isomers II and III are more active toward hydrolysis than compound V ($k_2$ = 0.195 liter/mole•sec) [11]. This can be explained in two ways: first of all, by the higher electronic density at $C_\beta$ in the initial state, and secondly, by the greater amount of delocalization of the positive charge in the transition state. Both of these effects would be exerted in the same direction. Unfortunately, it was not possible for us to compare directly the activities of compounds II, III, and I toward hydrolysis, although, according to data published previously [6], 10-vinylphenothiazine is more than three orders of magnitude more active than compound V and would thus be expected to be more reactive (toward hydrolysis) than compounds II or III.

As can be seen from the data in Table 2, the trans-isomer III is more reactive toward hydrolysis than its cis-isomer II. The reduced reactivity of cis-isomers compared to their trans-isomers has also been observed in the case of 9-alkenylcarbazoles [11], and has been associated with a diminished p-π conjugation effect due to steric repulsion of the substituents in the cis-orientation, which distorts the coplanarity of the C=C bond and the heterocyclic portion of the molecule. It is significant that the reactivity differences between the cis- and trans-isomers level off in the transition from 9-alkenylcarbazoles to 10-alkenylphenothiazines, which would appear to be the result of the specific three-dimensional structure of the phenothiazine ring [8, 9], which leads to lower steric strain in compound II and thus also reduces the activity difference between compounds II and III with respect to hydrolysis.

## EXPERIMENTAL

PMR spectra were recorded on a BS-487C spectrophotometer (in $CDCl_3$), IR spectra were taken on a Specord 71 IR spectrophotometer (using KBr pellets), and UV spectra were recorded on a Specord M-40 spectrophotometer (in hexane) at concentrations of $2.19 \cdot 10^{-5}$ ($\lambda_{max}$ 256 nm) and $1.09 \cdot 10^{-4}$ ($\lambda_{max}$ 303 nm) for compound II, and $2.52 \cdot 10^{-5}$ M for compound III. TLC was carried out on Silufol plates. Kinetics experiments of hydrolysis reactions were run by measuring the amount phenylacetaldehyde released; it was analyzed by basic oximation carried out using hydroxylamine [14]. UV spectroscopy, which is generally used for these types of analyses, could not be used due to overlap of the absorptions due to the carbonyl groups in the aldehyde product and in the starting materials, compounds II and III.

cis-10-(2-Phenylvinyl)phenothiazine (II). A three-necked flask was charged successively with 4 g (20 mmole) phenothiazine, 50 ml DMSO, and 1 g (180 mmoles) of powdered KOH. The mixture was heated to 100°C, and after 30 min, 4.4 ml (40 mmoles) of phenylacetylene was added slowly dropwise to the mixture. The reaction solution was stirred vigorously for 2 h at 100°C. The course of the reaction was monitored by TLC using hexane–ether, 6:1. After reaction was complete, the solution was cooled and poured onto 250 ml water. The resulting dark orange precipitate was removed by filtration and washed several times with water until it was neutral. The precipitate was dried completely on the filter and washed with acetone (three times, with 20 ml portions). The precipitate was then recrystallized threefold from ethanol to give 3.38 g (56%) of white needle-shaped crystals.

trans-10-(2-Phenylvinyl)phenothiazine (III). A. The acetone filtrate (from the preceding experiment) was evaporated and the residue was distilled at 245-248°C (6.65 hPa) to give 1.05 g (18%) of a yellow substance which crystallized in the receiver. Recrystallization from ethanol gave white needle-shaped crystals.

B. A test tube was charged with 1 g (3 mmoles) of compound, stoppered, and heated at 200°C for 4 h. The reaction mixture was cooled to 20°C, and the resulting solid mass was crystallized from acetone. Yield, 0.96 g (96%) of compound III in the form of white needle-shaped crystals.

Acidic Hydrolysis of cis-10-(2-Phenylvinyl)phenothiazine (II). A test tube containing 30 ml of a 0.003 M solution of compound II in 60% (by volume) aqueous dioxane was treated with 0.2 ml of 0.1 N HCl as catalyst. The solution was allowed to stand at room temperature for 14 h. TLC of the reaction mixture in hexane–ether, 6:1, indicated the absence of starting material II ($R_f$ 0.4) and the presence of phenothiazine ($R_f$ 0.16).

Kinetic Measurements. A known weight of starting material was dissolved in aqueous dioxane in a volumetric flask to 50 or 100 ml (the solubility at 60°C is not greater than $3.1 \cdot 10^{-3}$ M). A 10 ml sample of solution was transferred to a test tube, and a small amount of dioxane (0.15-0.45 ml) was added to each sample so as to maintain the correct solvent composition after addition of catalyst. The sample test tube was then placed in a thermostatted bath. The catalyst solution was introduced to the test tube using a micropipet. After the required period of time, the test tube was removed from the oven and cooled in ice for 40-50 sec in order to effect rapid quenching of the reaction. Each sample test tube was then treated with 5 ml of a hydroxylamine solution (prepared by mixing 2.3 ml of 1 N $NH_2OH \cdot HCl$, 0.8 ml of 2 N KOH, and 75 ml of water), the walls of the test tube were washed down with 2 ml of water. The test tubes were then maintained at 20°C for 2 h and 30 min in order to achieve complete oximation of phenylacetaldehyde. The contents of the test tubes were then titrated with 0.01 N HCl on a EV-74 potentiometer to the inflection point on the titration curve for free hydroxylamine with 0.01 N HCl in the given reaction medium. A blank experiment was run parallel to each trial. For every temperature value studied, a series of experiments involving three separate catalyst concentrations was conducted. Rate constants were calculated by integration of the equations for a pseudo-first order reaction. Linear first order rate dependences versus catalyst concentration were observed in all of the series of experiments. The angular coefficient for each of these rate dependences, calculated by least squares, was accepted as the true value of the second order hydrolysis rate constant at a given temperature.

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