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10-ALKENYLPHENOTHIAZINES.

1. SYNTHESIS AND CIS,TRANS-ISOMERIZATION OF 10-PROPENYLPHENOTHIAZINES

V. A. Anfinogenov, O. A. Napilkova, E. E. Sirotkina, V. D. Filimonov, and V. D. Ogorodnikov

UDC 547.869.2:542.952.4:541.634

A study was carried out on the isomerization of 10-allylphenothiazine (I) in DMSO by the action of t-BuOK, KOH and NaOH. The isomerization proceeds stereospecifically at room temperature by the action of t-BuOK at an elevated temperature by the action of KOH and NaOH to give cis-10-propenylphenothiazine (II). The effect of the t-BuOK concentration, temperature and reaction time on the isomeric composition of the 10-propenylphenothiazines formed was studied. Under conditions of kinetic control, I gives II, which isomerizes under the reaction conditions to give an equilibrium mixture of cis- and trans-10-propenylphenothiazine with 44-45% trans isomer III. The isomerization temperature has virtually no effect on the II/III isomer ratio.

Of the N-akenylphenothiazines, only N-vinylphenothiazine has been studied in considerable detail [1-3], while the homologs of this compound have not been described in the literature. There has only been mention of 10-propenylphenothiazine obtained by the multistep procedure in the proof of the structure of the product of the alkylation of phenothiazine by 1-chloro-2-dimethylaminopropane [4].

The base-catalyzed isomerization of N-allylamines is commonly employed in preparative organic chemistry to obtain N-allylamines [5] but this reaction has not been studied for thiazines.

In order to obtain 10-propenylphenothiazine, we studied the isomerization of 10-allylphenothiazine (I) in DMSO by the action of t-BuOK, KOH and NaOH.

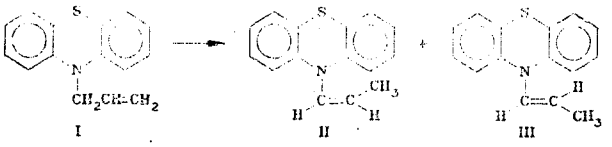
I. I. Polzunov Altai Polytechnical Institute, Barnaul 656099. Tomsk Institute of Petroleum Chemistry, Siberian Division, Academy of Sciences of the USSR, Tomsk 634055 and S. M. Kirov Tomsk Polytechnical Institute, Tomsk 634004. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 121-124, January, 1986. Original article submitted November 21, 1984.

 0009-3122/86/2201-0100$12.50

TABLE 1. Dependence of the Composition of the Isomer Mixture of Propenylphenothiazines II/III on Time and Temperature Upon the Isomerization of I ([I]$_0$ =

Temperature, °C	Time, min	II/III isomer ratio, %
50	300	100/0
70	10	84/16
	60	69/31
	180	62/38
	300	61/39
80	10	77/23
	120	59/41
	300	56/44
100	10	71/29
	180	56/44
	300	57/43
150	10	60/40
	180	54/46
	300	54/46

*Here and subsequently, 0.717 N solution in t-BuOH.



The isomerization both by the action of t-BuOK and KOH or NaOH gives the complete conversion of phenothiazine I to a mixture of isomers II and III; other products were not detected. In the presence of t-BuOK, the reaction rate reaches a maximum at a catalyst concentration of 0.15 mole/liter and the reaction is complete in this case in 15 min. The effect of the amount of catalyst on the time required for total conversion of phenothiazine I at room temperature as determined by thin-layer chromatography is given below. The time for total conversion is 4320, 75(65) and 15 min for 0.049, 0.083, and 0.15 mole/liter t-BuOK.

PMR spectroscopy at room temperature indicates that the reaction proceeds with high steric specificity to form exclusively cis isomer II. This finding distinguishes this reaction in the phenothiazine series from the isomerization of dialylallyamines [6] and 9-allylcarbazoles [7], in which the isomeric purity of the cis-isomers is not greater than 90%. As shall be shown below, this is apparently related to the greater thermodynamic stability of cis-isomer II relative to the trans isomer III.

The effect of temperature and reaction time on the ratio of isomers II and III was evaluated relative to the integral intensities of the methyl group signals in the PMR spectra (Table 1). The trans isomer III appears in the reaction mixture at 70°C and its content after 5 h reaches 39%. A further increase in the reaction temperature to 150°C increases the content of III to 44-46%. The II $\rightleftarrows$ III equilibrium is reached 3-5 h after the onset of the isomerization and, within experimental error, temperature has virtually no effect on the equilibrium constant (K) which was found to be 0.82 ± 0.03 (ΔG_{100} = 0.62 ± 0.11 kJ/mole). We note that thin-layer chromatography indicates the absence of starting compound I in the reaction solution. Under analogous conditions, pure cis isomer II gives a mixture of cis and trans isomers II and III with approximately the same composition. Hence, under kinetically controlled conditions, allylphenothiazine forms II which isomerizes under the reaction conditions to an equilibrium mixture of the cis and trans isomers, II and III.

The high thermodynamic stability of cis isomer II relative to trans isomer III distinguishes 10-propenylphenothiazine from previously studied 9-propenylcarbazoles, for which the cis isomer is less stable than the trans isomer due to steric interaction of the methyl group and the planar carbazole ring [7] . Our results indicate that the steric interaction

TABLE 2. Conditions for the Preparation of cis-10-Propenylphenothiazine II

I*, mole	Catalyst (mole)	Temperature, °C	Time,† min	Yield of II, %
0,063	*t*-BuOK ($1{,}6 \cdot 10^{-2}$)	25	15	89
0,01	*t*-BuOK ($4{,}9 \cdot 10^{-4}$)	50	10	—
0,002	KOH ($8{,}9 \cdot 10^{-4}$)	25	3600	—
0,002	KOH ($8{,}9 \cdot 10^{-4}$)	100	270	—
0,251	KOH ($2{,}1 \cdot 10^{-2}$)	60	30	68
0,013	NaOH ($1{,}5 \cdot 10^{-2}$)	60	60	64

*5 ml DMSO per g I.
†Reaction time corresponding to complete conversion of I.

TABLE 3. Spectral Characteristics of 10-Propenylphenothiazines

Compound	PMR spectrum (CCl_4)*				IR spectrum ‡, cm^{-1}	
	Chemical shifts, δ, ppm †, J, Hz					
	H_α	H_β	CH_3	H_α–H_β	$\nu_{C=C}$	δ-CH
II	6,16, d	5,6, m	1,55, d	7,0	1657	945
III	6,29, d	5,6, m	1,68, d	13,0	—	—

*For compounds II and III, the SSCC are: J H_β, CH_3 = 7.0, J H_α, CH_3 = 1.5 Hz.
†The signals of the phenothiazine protons form a multiplet at 6.5-7.1 ppm.
†The IR spectrum of II is completely identical to the spectrum of the mixture of II and III.

of the methyl group and the phenothiazine system in cis-10-propenylphenothiazine is absent or very weak compared to cis-9-propenylcarbazole.

This decrease in the steric strain in II is likely a consequence, firstly, of the nonplanar structure of the phenothiazine system [8] and the quasiaxial orientation of the substituent at the nitrogen atom (extra configuration [9]). It is quite obvious that the steric interaction in the extra configuration between the cis-methyl group and the hydrogen atom at $C_{(1)}$ of the nonplanar heterocyclic fragment in isomer II is less pronounced than in planar cis-9-propenylcarbazole. Secondly, we should recall that the participation of the nitrogen unshared electron pair in the extra configuration to the total π-electron conjugation is reduced [10] and, thus, some twisting of the phenothiazine system in II about the C–N bond leads to a significant suppression of p–π conjugation [7, 11].

The high thermodynamic stability of cis isomer II relative to the trans isomer of 10-propenylphenothiazine permits us to categorize 10-propenylphenothiazines as "anomalous" olefins, whose cis isomers are more stable than their trans isomers despite steric strain [12-15]. Unfortunately, we are not able to give an unequivocal explanation for this interesting finding.

This reaction is efficiently catalyzed by KOH and NaOH in DMSO. We should note that, in contrast to t-BuOK, the isomerization of phenothiazine I in the presence of KOH and NaOH proceeds stereospecifically both at room temperature and at 100°C. Although the catalytic activity of KOH and NaOH is much less than that of t-BuOK (Table 2), these hydroxides are conveniently used for the preparation of cis-10-propenylphenothiazine II to their availability and ease in handling.

The structures of 10-propenylphenothiazines II and III were demonstrated using IR and PMR spectroscopy. The spectral parameters are given in Table 3.

EXPERIMENTAL

The IR spectra were taken neat on a IKS-29 spectrometer. The PMR spectra were taken on a BS-487C spectrometer in CCl_4. In the study of the effect of the reaction conditions for

the isomerization of I on the ratio of isomers II and III, the spectra were taken in benzene. Phenothiazine I was prepared according to the method of Simov and Kamenov [16].

cis-10-Propenylphenothiazine (II). A sample of 31 ml 0.51 N t-BuOK in t-BuOH was added to a solution of 15 g (63 mmoles) 10-allylphenothiazine I in 75 ml dry DMSO and the mixture was maintained at room temperature for 15 min. The reaction was monitored using thin-layer chromatography on Silufol plates with 6:1 hexane–ether as the eluent. After the complete conversion of I, the solution was poured into water. The precipitated oil was extracted with benzene. The benzene layer was washed with water and dried over potassium carbonate. PMR spectroscopy indicated that the solution contained cis isomer II. Vacuum distillation and crystallization from ethanol give 13.4 g (89%) cis-10-propenylphenothiazine as white needles with mp 34-35°C, bp 182-184°C (4 hPa). Found: C 75.4; H 5.3; N 6.0; S 13.2%. Calculated for $C_{15}H_{13}NS$: C 75.2; H 5.4; N 5.9; S 13.4%.

Mixture of cis-10-propenylphenothiazine (II) and trans-10-Propenylphenothiazine (III). A sample of 5 g (21 mmoles) I and 7 ml 0.69 N t-BuOK in t-BuOH in 25 ml dry DMSO was maintained at 100°C for 1 h. The isolation of the products was carried out by analogy to the previous procedure. Vacuum distillation at 191-193°C (5-7 hPa) gave 3.9 g (78%) of a yellow oil. PMR spectroscopy indicated that the mixture of isomers II and III was 54:46. Isomer III could not be isolated from the mixture.

The reaction in the presence of KOH and NaOH was carried out by analogy to the above procedure under the conditions indicated in Table 2. Samples of powdered KOH and NaOH were used.

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