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SYNTHESIS AND ANTICONVULSANT ACTIVITY OF cis- AND TRANS-ISOMERS OF 10-PROPENYL- AND 10-(PHENYLVINYL) PHENOTHIAZINES

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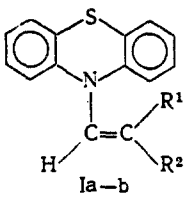
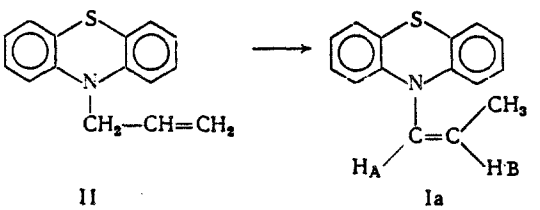
The present study describes the synthesis and results of testing the anticonvulsant activity of 1-alkenylphenothiazines (Ia-c) in comparison to 10-allylphenothiazine (II) and unsubstituted phenothiazine (III).



Ia—b

Ia: $R^1=CH_3$, $R^2=H$; Ib: $R^1=Ph$, $R^2=H$; Ic: $R^1=H$, $R^2=Ph$.

Compound Ia was obtained by the isomerization of II in DMSO by the action of potassium tert-butylate.



II Ia

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With the K tert-butylate reactant the reaction proceeds at room temperature stereoselectively with the exclusive formation of the cis-isomer of Ia at a yield of 89%. An increase in the reaction temperature results in the formation of trans-10-propenylphenothiazine along with compound Ia. NMR data indicate that the former accounts for 30 to 45% of the isomer mixture. These results demonstrate that as in the case of 9-allylcarbazol isomerization [4], the formation of the cis-isomer of Ia takes place in a kinetically controllable stage with the subsequent slow isomerization of the latter into the trans-isomer.

We obtained the cis and trans-isomers of 10-(2-phenylvinyl) phenothiazine Ib by reacting phenothiazine with phenylacetylene in a superbase medium consisting of KOH in DMSO.

Phenothiazine was quantitatively added to phenylacetylene at a temperature of 100°C and higher with the formation of the cis-isomer Ib in a kinetically controlled reaction. We utilized the variable solubility of the Ib and Ic isomers in acetone in order to separate them. The cis-isomer Ib can be completely converted to the trans-isomer Ic by heating in the absence of a solvent at 200°C.

The structure of the synthesized compounds was confirmed by element analysis and IR, UV, and PMR spectral analysis.

EXPERIMENTAL CHEMICAL

IR spectra were recorded on a Specord-71R instrument (GDR) in KBr pellets. UV spectra were read on a Specord-M40 spectrophotometer (GDR) in hexane. PMR spectra were read on a BS 487C spectrophotometer (Czechoslovakia) in CCl_4 for compound Ia and in $CDCl_3$ for compounds Ib, c. Internal standard was HMDS. Compound II was obtained by method [3].

cis-10-2-(Phenylvinyl)phenothiazine (Ib). A 31-ml portion of 0.51 N solution of K tert-butylate was added to a solution of 15 g (75 mmole) of compound II in 75 ml of dry DMSO. The solution was kept at room temperature for 15 min until the initial compound II was completely converted. Reaction progress was controlled on Silufol plates (6:1 hexane–diethyl ether). The reaction solution was decanted into water and the precipitated oil was extracted by benzene, washed with water, and dried with potash. After the benzene was distilled off, the product was vacuum redistilled at 182-184°C (3 mm Hg) and 13.4 g (89%) of cis-10-propenylphenothiazine was distilled off in the form of a yellowish oil which crystallized upon standing. After recrystallization from ethanol compound Ia was obtained as white needle-shaped crystals with a mp of 34-35°C. Found %: C 75.4; H 5.3; N 6.0; S 13.2. $C_{15}H_{13}NS$. Calculated %: C 75.2; H 5.4; N 5.9; S 13.4. IR spectrum, ν, cm^{-1}: 1657 (C=C); 945 (=CH). UV spectrum, λ_{max}, nm (log ε): 256 (4.61), 312 (3.62). PMR spectrum, ppm: 6.27 d. ($1H_A$, $J_{H_A-H_B}$ = 7 Hz), 5.6 m ($1H_B$), 1.56 d (3H, $J_{CH_3-H_B}$ = 7 Hz, $J_{CH_3-H_A}$ = 1.5 Hz), 6.5-7.1 m (8H protons of the phenothiazine ring).

cis-10-(2-phenylvinyl)phenothiazine (Ib). A 1-g (18-mmole) portion of powdered KOH was added to a solution of 4 g (20 mmole) of phenothiazine in 50 ml of DMSO and then with vigorous stirring 4.4 ml (40 mmole) of phenylacetylene was added dropwise over a period of 30 min at 100°C. The reaction mixture was stirred for 2 additional h, then cooled, and decanted into 250 ml of water. The resultant dark brown precipitate was filtered off, washed with water until neutral, and then dried. The precipitate on the filter was washed off with acetone (3 × 20 ml), and the residue was triple crystallized form ethanol. The yield of cis-10-(2-phenylvinyl)phenothiazine was 3.38 g (56%) in the form of white needle-shaped crystals with mp 140-141°C. Found %: C 79.6; H 5.1; N 4.6; S 10.3. $C_{20}H_{15}NS$. Calculated %: C 69.0; H 5.0; N 4.7; S 10.6. IR spectrum, ν, cm^{-1}: 1640 (C=C), 915 (=C). UV spectrum, λ_{max}, nm (log ε): 256 (4.63), 303 (3.89), 333 (3.76). PMR spectrum, ppm: 6.3 d ($1H_B$, $J_{H_B-H_A}$ = 8.5 Hz), 6.5 d ($1H_A$ = $J_{H_A-H_B}$ = 8.5 Hz), 6.5-7.6 μ (13H-protons of the phenyl and phenothiazine rings).

trans-10-(2-Phenylvinyl)phenothiazine (Ic). A 1-g (3-mmole) portion of compound Ib was kept in a closed test tube for 4 h at 200°C. After cooling, the solid reaction mass was crystallized from acetone. The yield of trans 10-(2-phenylvinyl)phenothiazine was 0.96 g (96%) in the form of needle-shaped crystals with mp 169-170°C. Found %: C 79.6; H 5.4; N 4.7; S 10.4. $C_{20}H_{16}NS$. Calculated %: C 79.7; H 5.0; N 4.7; S 10.6. IR spectrum, ν, cm^{-1}: 1650 (C=C), 920 (=CH). UV spectrum, λ_{max}, nm (log ε): 258 (4.48), 308 (4.35), 333 (4.24). PMR spectrum, ppm: 6.3 d ($1H_B$, $J_{H_B-H_A}$ = 14.5 Hz), 6.5-7.6 m ($1H_A$ + 13H-protons of phenyl and phenothiazine rings).

TABLE 1. Pharmacological Properties of Phenothiazine Derivatives

Index	Dose, mg/kg	Ia	Ib	Ic	II	III
Acute toxicity - LD_{50}, mg/kg		1000	1000	1000	1000	1000
LD_{50}/ED_{50} (RTA)		13,3	5,0	5,0	7,1	3,8
Percent of anticipatory convulsions during MES	100	33,3	33,3	16,7	33,3	...
	200	60,0	50,0	50,0	66,7	16,7
	300	...	...	...	...	66,7
Percent of animals surviving MES	100	33,3	16,7	16,7	83,3	...
	200	60,0	50,0	50,0	66,7	83,3
	300	...	...	...	...	100,0
ED_{50}, mg/kg		75 (45,4—123,8)	200 (121,2—330)	200 (121,2—330)	140 (93,3—210)	262 (218,3—314,4)
Corazole convulsion threshold, mg/kg	200	107,1±9,3 (0,846)	68,7±15,6 (0,258)	117,3±9,6 (0,102)	122,9±8,9 (0,044)	100,0±7,4 (0,500)
Anticorazole index		1,03	0,75	1,28	1,34	1,09
Effect on movement coordination:						
Initial background	100	...	...	....	....	...
after 30 min	...	...	...	33,3	...	...
after 60 min		...	.....	16,7	...	...
after 120 min		...	16,7	16,7	...	...
Effect on body temperature:						
initial background	100	36,3±0,46	36,5±0,42	35,2±0,32	37,5±0,39	...
after 30 min		36,0±0,49 (0,442)	36,3±0,42 (0,389)	36,1±0,46 (0,031)	36,2±0,38 (0,052)	...
after 60 min		35,6±0,21 (0,144)	35,9±0,35 (0,102)	36,0±0,25 (0,004)	36,9±0,28 (0,258)	...
after 120 min		35,5±0,32 (0,102)	36,0±0,46 (0,389)	35,6±0,42 (0,192)	35,9±0,28 (0,011)	...
Effect on electropain sensitivity threshold, B:						
initial background	100	12,3±0,71	10,2±0,71	10,7±0,88	10,2±0,53	...
after 30 min		11,5±0,7 (0,0628)	10,8±0,53 (0,223)	9,3±0,53 (0,141)	11,2±0,53 (0,141)	...
after 60 min		9,3±0,35 (0)	9,0±0,35 (0,195)	8,8±0,53 (0,012)	11,3±0,53 (0,141)	...
after 120 min		8,5±0,53 (0)	10,0±0,06 (0,845)	9,2±0,71 (0,192)	12,5±0,53 (0,016)	...

Note: The value P, reliability of differences in comparison to the control, is given in parentheses [2].

EXPERIMENTAL PHARMACOLOGICAL

The neurotropic properties of the phenothiazine derivatives Ia-c and compound II were studied in comparison to phenothiazine (III) on mongrel mice weighing 18 to 23 g. A total of 120 mice were used in the experiments (each dose was given to six animals). The compounds were administered orally in the form of a 1% starch mucilage suspension. The anticonvulsant activity was evaluated by the maximum electric shock test (MES) [7] and by the change in the Corazole tremor threshold [6]. This was followed by statistical processing by the nonlinear differences method [2]. The anticonvulsant properties were compared by the ED_{50} value which was found by the Litchfield and Wilcoxon method [1], the defense index (TD_{50}/ED_{50}, the range of therapeutic action (RTA) ($<D_{50}/ED_{50}$) and by the antiCorazole index. In addition, we examined the effect of the preparations on coordination of movement by the rotating rod test [5], the rectal temperature, and theelectro-pain sensitivity threshold, as well as the acute daily toxicity.

It is apparent from the table that the examined compounds exhibit a comparatively low level of toxicity (LD_{50} > 1000 mg/kg). At a dose of 100 mg/kg (1.5 to 2 h after administration), the preparations exhibited weak anticonvulsant properties in the MES test and a pronounced depressant effect in the Corazole test in the case of compound II (antiCorazole index 1.34). The anticonvulsant effect increased as the dosage was raised. It was most pronounced in compounds Ia (ED_{50} 75 mg/kg) and II (ED_{50} 140 mg/kg). That value was 200 mg/kg for the remaining compounds. For compound III it was 262 mg/kg. With the exception of compound Ib (at the 120th minute) and Ic (throughout the experiment) the preaprations did not exhibit myorelaxant activity. A statistically reliable hypothermic effect was manifested by compound Ic (30 and 60 minutes after administration) and II (120 minutes after administration) whereas preparations Ia and Ic, conversely, reduced the mice's sensitivity to electropain stimulation.

Thus, the results of our investigation shows that compound Ia and II exhibit anticonvulsant activity. In addition, compound II exhibits hypothermic and analgesic activity as well.

Our results allow us to conclude that anticonvulsant activity is increased when phenothiazine is converted to 10-allylphenothiazine and subsequently to the 10-alkenylphenothiazines.

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