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# SYNTHESIS AND ANTITREMOR PROPERTIES OF 4-PHENYLTHIOSEMI-CARBAZONES OF 5-SUBSTITUTED 2-AMINOBENZOPHENONES

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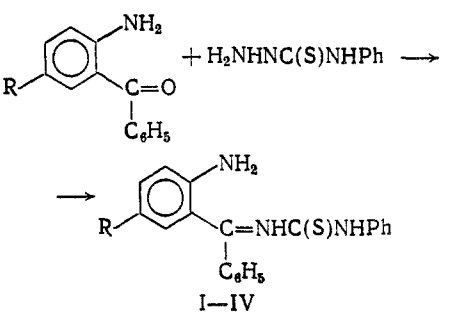
The antitremor properties of the thiosemicarbazones have been established from corazole antagonist and protection against maximum electric shock (MES) test [1, 5, 6]. However, there is no information in the literature on the ability of thiosemicarbazones to prevent the convulsive effect of thiosemicarbazide itself. In order to find new more effective antitremor agents and to clarify certain aspects underlying the mechanism of antitremor agents, we synthesized 4-phenylthiosemicarbazones of substituted 2-aminobenzophenones and investigated their antitremor properties.

4-phenylthiosemicarbazones of benzophenones (I-IV) were synthesized by condensing 4-phenylthiosemicarbazone with 5-substituted 2-aminobenzophenones in the presence of HCl (Table 1).




I—IV

R = $CH_3$ (I), Cl (II), Br (III), $NO_2$ (IV)

The structure of compounds I-IV was established by IR-, UV-, PMR-spectroscopy, mass spectrometry, and x-ray structure analysis. Syn-isomers were shown to be the result of the condensation reaction [3].

A study of the antitremor properties of I-IV demonstrated that at a dose of 10 mg/kg those compounds protected animals against 40-50% of thiosemicarbazide (TSC)-induced convulsions. All of the tested compounds exhibited a high degree of activity. Moreover, their protective effect was almost doubled when the dosage was increased by 50 mg/kg (Table 2). At significantly higher doses (50-100 mg/kg) compounds I-IV protected animals against 50-90% of MES-induced tonic-extensor tremors. Compounds I-IV exhibited a weak anticorazole effect and offered no protection against strychnine-induced (2.5 mg/kg) tremors.

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TABLE 1. 4-Phenylthiosemicarbazones of 5-Substituted 2-Aminobenzophenones I-IV

| Compound | Yield, % | mp, °C | $R_f$ | Empirical formula |
|---|---|---|---|---|
| I | 77 | 164—166 | 0.66 | $C_{21}H_{20}N_4S$ |
| II | 73 | 166—168 | 0.58 | $C_{20}H_{17}ClN_4S$ |
| III | 70 | 190—193 | 0,57 | $C_{20}H_{17}BrN_4S$ |
| IV | 67 | 210—215 | 0.39 | $C_{20}H_{17}N_5O_2S$ |

TABLE 2. Antitremor Activity (in %) of Compounds I-IV

| Compound. | Dose, mg/kg | Corazole, 130 mg/kg (s/c) | Thiosemicarbazide, 27 mg/kg (i/p) | Strychnine, 2.5 mg/kg (s/c) | MES |
|---|---|---|---|---|---|
| I | 25 | 16 | 50 | 16 | 40 |
| | 100 | 16 | 90 | 16 | 50 |
| II | 10 | 16 | 40 | 16 | 10 |
| | 50 | 16 | 90 | 16 | 90 |
| | 100 | 34 | 90 | 16 | 90 |
| III | 10 | 16 | 50 | 16 | 10 |
| | 50 | 16 | 90 | 16 | 50 |
| | 100 | 34 | 90 | 16 | 90 |
| IV | 10 | 16 | 40 | 16 | 10 |
| | 80 | 16 | 90 | 16 | 50 |
| | 100 | 16 | 90 | 16 | 50 |
| Control | — | 16 | 10 | 16 | 10 |

Note. i/p denotes intraperitoneal administration, s/c means subcutaneous administration.

TABLE 3. PMR-Spectra of Compounds I-IV (in $CDCl_2$)

| Compound | Chemical shift, δ, ppm | | | |
|---|---|---|---|---|
| | C—H (arom.) | N—H | $NH_2$ | $CH_3$ |
| I | 7,50—6,51(m, 13H) | 9,33(s,1H), 8,70(s,1H) | 3,36(s,2H) | 2,15 (s, 3H) |
| II | 7,51—6,53(m, 13H) | 9,33(s,1H), 8,62(s,1H) | 3,60(s,2H) | — |
| III | 7,51—6,55(m, 13H) | 9,33(s,1H), 8,63(s,1H) | 3,63(s,2H) | — |
| IV | 8,05—6,81(m, 13H) | 10,13(s,1H), 9,95(s,1H) | 3,8 (s,2H) | — |

TABLE 4. IR-, UV-Spectra of Compounds

| Compound | IR-spectra, $cm^{-1}$ | | | | UV-spectra (ethanol) |
|---|---|---|---|---|---|
| | N—H | C=S | C=N | solvent | $\lambda_{max}$, nm, log ε |
| I | 3316 (80); 3384 (67); 3470 (63) 3200 (52); 3330 (81); 3460 (54) | 1629 (65) | 1600 (65) 1603 (48) | $CCl_4$ KBr | 207 (4,64); 234 (4,44); 320 (4,46) |
| II | 3310 (80); 3384 (52); 3470 (35) 3200 (56); 3310 (68); 3335 (65) 3460 (53) | 1628 (52) | 1595 (60) 1628 (52) | $CCl_4$ KBr | 204 (4,50); 220 (4,37); 310 (4,39); 365 (4,94) |
| III | 3325 (65); 3384 (38); 3467 (30) 3205 (54); 3230 (53); 3335 (75) 3465 (46) | 1629 (56) | 1605 (40) 1602 (38) | $CCl_4$ KBr | 206 (4,60); 235 (4,41); 318 (4,43) |
| IV | 3305 (73); 3375 (32); 3455 (26) 3186 (56); 3250 (54); 3303 (68) 3455 (52) | 1632 (82) | 1610 (55) 1602 (48) | $CCl_4$ KBr | 204 (4,63); 232 (4,42); 317 (4,45) |

Note: percent absorption in parentheses.

While exhibiting less effective antitremor activity than the established anticonvulsants, at high doses (100-500 mg/kg) compounds I-IV did not exhibit sedative and myorelaxant activity and did not disrupt motor coordination.

In connection with the fact that in our experiments compounds I-IV were more effective for preventing the tremor effect of thiosemicarbazide, an inhibitor of the enzyme glutamate decarboxylase (GDC; Pharmacopoeia code 4.1.1.15) which is responsible for maintaining a constant level of GABA (gamma amino butyric acid) in the brain [4], one can assume that the increase in brain GABA during GABA-deficient tremors underlies the mechanism of compound I-IV action, i.e., GDC stimulation occurs.

The semicarbazones I—IV we investigated exhibited low toxicity ($LD_{50}$ higher than 900 mg/kg). 4-phenylthiosemicarbazide itself at doses of 100 mg/kg induced prolonged slight tremors lasting 2 h. When administered in combination with compound III at a dose of 50 mg/kg it accorded 80% protection against tremors. At doses of 500 mg/kg 4-phenylthiosemicarbazide strong myorelaxant activity 40 min after administration. Compound III did not exhibit any myorelaxant properties at the same doses.

## EXPERIMENTAL (CHEMICAL)

**4-Phenylthiosemicarbazones of 5-Substituted 2-Aminobenzophenones.** A 0.01 mole portion of 4-phenylthiosemicarbazide and 0.01 mole of the corresponding 2-aminobenzophenone was dissolved in 150 ml of ethyl alcohol. A 5 ml portion of ethyl alcohol saturated with HCl was added and the mixture was boiled for 3 h in a reflux condenser. The resultant light brown precipitated crystals were filtered off and crystallized from ethyl alcohol. The pure substances were dyed yellow. The yield and constants of the synthesized compounds are given in Tables 1, 3, and 4. Element analysis data satisfied the calculated values. The structure of the synthesized substances was established by IR-, UV-, PMR-spectroscopy, and x-ray structural analysis (see Tables 3 and 4) [3]. The IR-spectra of I-IV had absorption spectra in the 3200-3460 $cm^{-1}$ region for free and hydrogen-bound stretching vibrations of the N—H bonds of the thiocarbonyl group at 1629—1632 $cm^{-1}$, the C=N azomethine bond at 1595—1610 $cm^{-1}$, and other bands that are usually recorded for aromatic systems that confirm the structure of the indicated compounds. The UV-spectra exhibited three absorption bands (see Table 4): the first two are characteristic of benzene rings (204—207 and 220—232 nm), and the third — $\pi$—$\pi^*$ — are transitions of the azomethine bond conjugated with the aromatic chromophores.

The position and integral intensity of the proton signals in the PMR-spectra of compounds I—IV fully confirm their structure (see Table 3), and the position of the proton signals of the $NH_2$ group, in consideration of the literature data [3] clearly indicates the syn-configuration of the 4-phenylthiosemicarbazones of aminobenzophenones I—IV.

## EXPERIMENTAL (BIOLOGICAL)

The antitremor activity of compounds I—IV was tested on male mice weighing 18—20 g. The substances were administered ip in a suspension with Tween 80. The anticonvulsant effect of the compounds was studied on models of tremor states induced by corazole (130 mg/kg subcutaneously), thiosemicarbazide (27 mg/kg ip), strychnine (2.5 mg/kg subcutaneously), and maximum electric shock (MES) by method [2]. The sedative action was determined by the open field method, motor coordination disruption was measured by the "net-climbing" test, and myorelaxant activity was determined by the "rotating piston" test [2].

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