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# Pharmacological Activity of Bromo-Phenyl Derivatives of Substituted Pyrazoles

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**ABSTRACT**: New bromo derivatives of pyrazoles were synthesized, the anti-inflammatory activity of pyrazole derivatives of bromophenyl substituted phenols was studied, and the relationship between it and the structure of the obtained compounds was established. Their effect on the functions of various organs and systems, bioelectric activity of the heart, the action of analeptics of the central nervous system, hypnotics, and toxicity were also tested.

**KEY WORDS**: Derivatives of pyrazoles, Hexadiene esters of phenols, Diazomethane,The anti-inflammatory activity, Toxicity, Amidopyrine.

## I.INTRODUCTION

The search for new anti-inflammatory drugs to fight colds, flu and other diseases, as well as actions within the body, is very relevant.
In continuation of the work [1], we studied the dependence of the anti-inflammatory properties of pyrazoles of substituted oxymethylene phenyls on their structure.

## II. SIGNIFICANCE OF THE SYSTEM

The paper mainly focuses on how the chemistry derivatives of pyrazoles. The study of literature survey is presented in section III, Proposed methodology and discussion is explained in section IV, section V covers the experimental results of the study, and section VI discusses the future study and Conclusion.

## III. LITERATURE SURVEY

Given the literature data [2,3] on a wide spectrum of biological, pharmacological actions of bromo, iodine, and arylpyrazoles of substituted phenols, compounds with practically useful, low toxic, anti-inflammatory properties can be found. The synthesis of arylpyrazoles halogen substituted phenols is given in our earlier publications [4-12]. In connection with the foregoing, it seemed to us interesting to synthesize new bromo derivatives of pyrazoles, to study their pharmacological activity and to establish the relationship between it and the structure of the substance.

## IV. PROPOSED METHODOLOGY AND DISCUSSION

The object of the study was bromine derivatives of substituted of phenoxy pyrazoles. The progress of the reaction and the individuality of the compounds were monitored by TLC method on the second degree of activity, IR, PMR spectra and elemental analysis. IR spectrawere recorded on a VR-20 spectrometer. Laboratory tests of the obtained compounds for toxicity and anti-inflammatory activity were carried out on white mice.

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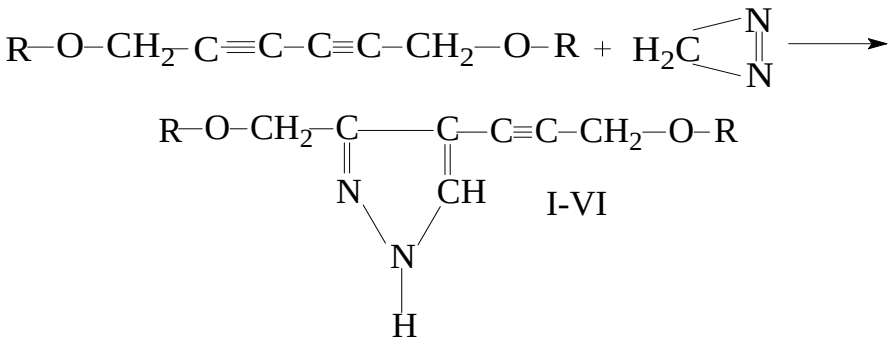
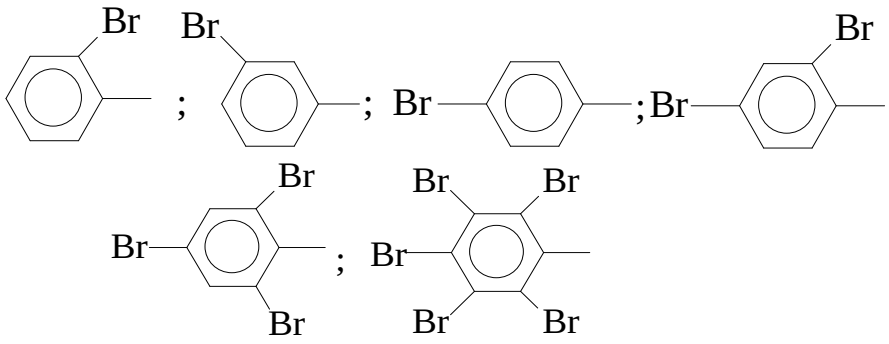
All compounds were obtained on the basis of the reaction of intermolecular cyclizations of symmetric 24 hexadiene esters of phenols with diazomethane, which was carried out at room temperature in a sulfuric ether medium according to the following scheme:



I-VI

where: R = 

Physico-chemical characteristics are given in table 1.

The individuality of the obtained compounds was checked by TLC method on the second degree of activity.
The structure was proved by the data of IR, PMR spectra and elemental analysis.

So, in the IR spectrum in the frequency range 3400–3300cm$^{-1}$, absorption bands appear, corresponding to the N–H groups of the pyrazole ring, vibrations of the pyrazole ring itself are observed in the region of 1540–1520 cm$^{-1}$.

In the PMR spectrum, two singlet signals are observed at 4,8–4,6 ppm, with a ratio of integrated intensities of 1,7 and 2,4. These signals are assigned to the protons of two methylene groups associated with the pyrazole ring and acetylene group, respectively. In the region of 6,9-7,5 ppm three groups of signals are observed, the sum of the relative intensities of which is 9,2, which corresponds to nine protons. The widest and strongest signal at 6,9 ppm with a multiplet structure is due to eight protons of two aromatic rings. Two weak signals at 7,15 and 7,50 ppm. correspond to the protons of the pyrazole ring and the proton of the N-H group.

The pyrazoles derivatives synthesized in this way were tested for toxicity and anti-inflammatory properties (Table 2).

Toxicity was studied on 150 white mice of both sexes weighing 18-24 g. The drugs were administered as a 1-10% oily solution subcutaneously. Preparations in each dose were tested on at least 6 animals. The volume of the injected solution did not exceed 1 ml.

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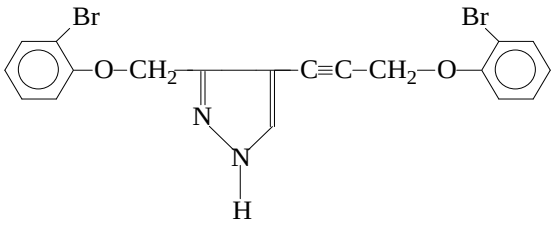
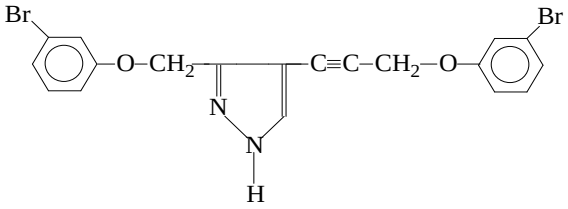
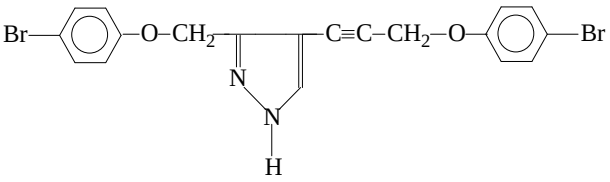
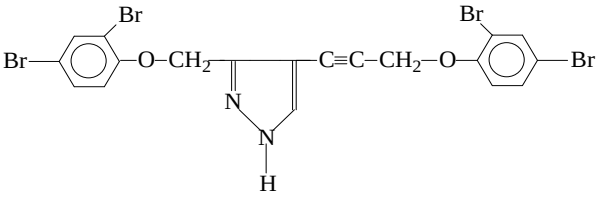
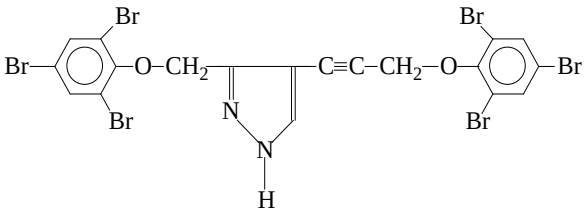
Table 1. Physico-chemical characterization of bromo derivatives of substituted phenoxy pyrazoles

| № p/p | Compound | Yield,% | MT,°C | Bruttoformula | Elemental analysis, % | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Calculated | | | Camputed | | |
| | | | | | C | H | N | C | H | N |
| I |  | 87,4 | 97-98 | $C_{17}H_{14}Br_2N_2O_2$ | 46,81 | 3,21 | 6,42 | 46,62 | 3,01 | 6,19 |
| II |  | 81,2 | 102-103 | $C_{17}H_{14}Br_2N_2O_2$ | 46,81 | 3,21 | 6,42 | 46,60 | 3,00 | 6,20 |
| III |  | 84,3 | 118-119 | $C_{17}H_{14}Br_2N_2O_2$ | 46,81 | 3,21 | 6,86 | 46,68 | 2,21 | 6,22 |
| IV |  | 85,2 | 124-125 | $C_{17}H_{12}Br_4N_2O_2$ | 33,40 | 3,65 | 4,65 | 33,68 | 3,41 | 4,47 |
| V |  | 86,8 | 157-158 | $C_{17}H_{10}Br_6N_2O_2$ | 27,24 | 1,33 | 3,74 | 27,09 | 1,19 | 3,50 |

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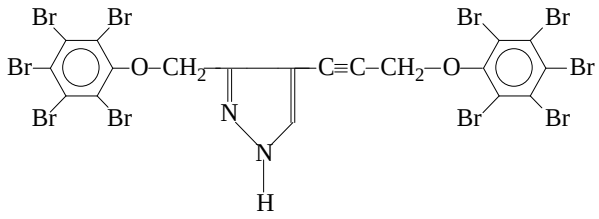
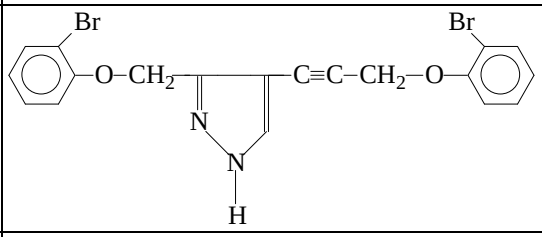
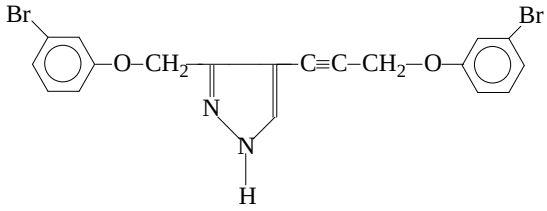
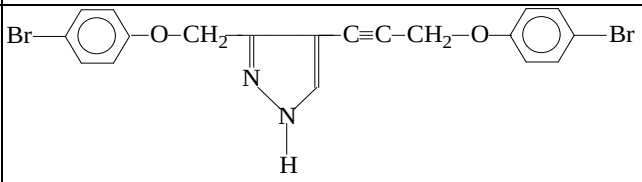
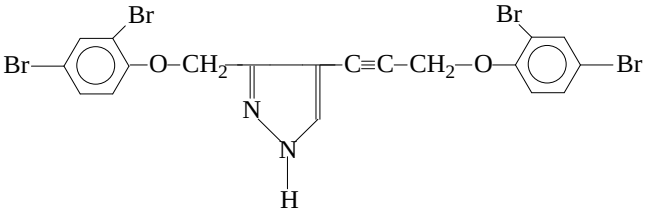
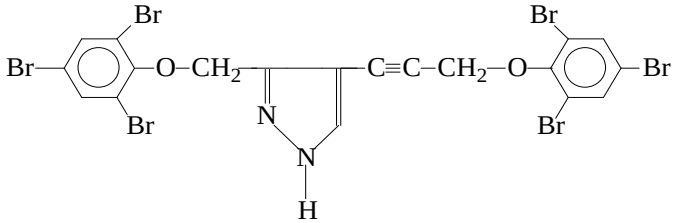
|---|---|---|---|---|---|---|---|---|---|---|
| VI |  | 88,5 | 185-186 | $C_{17}H_6Br_{10}N_2O_2$ | 19,26 | 0,56 | 2,64 | 19,03 | 0,41 | 2,40 |

Table 2. Anti-inflammatory activity of pyrazole derivatives of bromophenyl substituted phenols

| № p/p | Preparations | The anti-inflammatory activity, % | | | $M_м$ |
|---|---|---|---|---|---|
| | | 1/5L $D_{50}$ | 1/15LD $_{50}$ | Amidopyrine, 25 мд/kg | |
| I |  | 10,8 | 16,0 | 12 | 437,8 |
| II |  | 9,4 | 40,3 | 7,6 | 437,8 |
| III |  | 2,5 | 3,6 | 12,0 | 437,8 |
| IV |  | 0,7 | 0,9 | 18,4 | 595,6 |
| V |  | 0 | 0 | 7,6 | 753,4 |

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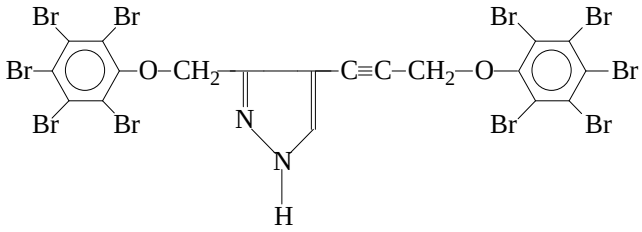
|---|---|---|---|---|---|
| VI |  | 0 | 0 | 7,6 | 1069,04 |

## V. EXPERIMENTAL RESULTS

### Synthesis of 3- (0-bromophenoxymethylene) -4 -(3 -0 –bromophenoxypropine) –pyrazole.

1,7 g of the starting diacetylene ether [1,6-bis- (ortho-bromophenoxy) -hexadiene-2,4] are introduced into a conical flat-bottomed flask, and then 0,92 g (0,02 g / mol) of a freshly prepared diazomethane solution is gradually introduced into 25 ml of sulfuric ether. The reaction mixture was kept in the dark at room temperature. As the yellow color of the solution becomes discolored, fresh portions of diazomethane are added until a stable yellow color is obtained. After that, the solvent was evaporated, and the product was purified by TLC method on $Al_2O_3$. The resulting product is a white crystals with a yellowish tint.

Yield 1,48 g (87,4 % of theory). Mp = 97-98 °C.
Under similar conditions, the remaining pyrazoles 2–6 were obtained (see Table 1).

## VI. CONCLUSION AND FUTURE WORK

With the introduction of the test substances in relatively small doses (50-200 ppm / kg), a decrease in motor activity is noted. A further increase in dose (1000-1500 ppm / kg) does not increase the state of oppression. Among the tested substances, preparations 4(2,4,6-tribromphenoxypropin-1)-3(2,4,6-tribromophenoxymethylene)-pyrazole and 4(2,3,4,5,6-pentabromophenoxy-propi-1)-3(2,3,4,5,6-pentabromophenoxymethylene)-pyrazoles in certain doses causes the death of animals. So, at a dose of 600 ppm / kg, fatalities are observed in two of the six mice, at a dose of 650 ppm / kg - in three of six, at a dose of 800 ppm / kg - in four of six, at a dose of 900 ppm / kg - in five of six. It should be noted that immediately before the death of animals, cramps are observed.

The mean lethal dose (LD50) was determined by the Litchfield-Wilcoxen method, $LD_{50}$ at $p=0,05 \cdot LD_{50}$ for 3- (2,4,6-tribromophenoxymethylene)-4-(2,4,6-tribromophenoxypropinyl) pyrozole (compound 5 ) was 740 ppm / kg.

It is established that the synthesized new drugs are low toxic. It should also be noted that the position of halogen (bromine) in the benzene ring does not significantly affect their toxicity. Experiments on the study of anti-inflammatory activity were carried out on 250 white mice weighing 120-200 g of both sexes. Inflammation was caused by formalin. Substances were administered subcutaneously as an oily solution 1 hour before the introduction of formalin.

The activity of the drug was compared with the action of the well-known anti-inflammatory drug - amidopyrine. Anti-inflammatory activity was determined by the oncometric method 3,6 and 24 hours after administration of formalin.

From the data given in Table 2, it can be seen that among the tested preparations, the drug 3(m-bromophenoxymethylene)-4-(3-m-bromophenoxy-propin-1) - pyrazole (2), which reduces inflammation by 40,3 %, has the most pronounced anti-inflammatory activity, while amidopyrine - only 8 %.

It should be noted that the position and number of substituents in the benzene ring affects the activity of the drugs. Thus, a pronounced anti-inflammatory effect is observed when bromine halogen is present in the m-position (40,3%), slightly lower in the 0-position (16%), and even less in the p-position (3,6%). With an increase in the number of halogens, the activity of the drugs decreases. The drug 2 was also tested on models of inflammation caused by various flagogenic agents.

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Inflammation was caused by subplanar insertion into the hind paw of 1 % formalin in the amount of 0,2 ml per animal. The activity was compared with butadione and hydrocortisone.

With subcutaneous administration, the drug, starting with a dose of 50 ppm / kg, has a pronounced anti-inflammatory effect. With the introduction of the drug in doses of 100 and 200 ppm / kg, the effect is 41 and 43 %, respectively.

Whis intraperitoneal administration, the drug (100 ppm / kg) and hydrocortisone (10 ppm / kg) have approximately the same anti-inflammatory activity: 39 and 37 %, respectively. Whis administration orally, the drug at a dose of 100 ppm / kg exhibits a more pronounced anti-inflammatory effect (25 %) than butadione (18 %) at a dose of 50 ppm / kg.

The effect of pyrazole II on inflammation with repeated oral administration was also studied. The studied drug, amidopyrine, butadion, hydrocortisone was administered 72, 48, 24 and 1 hour before the introduction of formalin. It was found that the drug at doses of 100 and 300 ppm / kg reduces formalin inflammation by 50 and 46 %, respectively, amidopyrine - by 37 %, butadione - by 45 %, hydrocortisone - by 50 %.

In the following series of experiments, inflammation was caused by dextran. The drugs were administered in the same dose and in the same sequence as with formalin inflammation. It was found that at doses of 100 and 300 ppm / kg, pyrazole II inhibits dextran inflammation by 35 and 24 %, respectively, while amidopyrine - by 32 %, hydrocortisone - by 34 %.

In inflammation caused by serotonin, the studied drug in doses of 100 and 300 ppm / kg inhibits serotin inflammation by 35 %, amidopyrine - by 30 %, hydrocartisone - by 30 %.

The effect of pyrazole II on motor-food reflexes was studied in a labyrinth on white rats weighing 150-200 g.

This drug was administered at doses of 50, 100 and 200 ppm / kg subcutaneously. It has been shown that it in doses causing an anti-inflammatory effect does not affect the higher nervous activity of animals, which should be considered as an advantage of this drug.

Experiments to study the effect of pyrazole 2 on the action of CNS analeptics were performed on 80 white mice of both sexes weighing 18-23 g. Of the analeptics, caffeine and corazole are used. The drug was administered subcutaneously at doses of 50, 100, 200 ppm / kg. Caffeine was administered subcutaneously at a dose of 400, and corazole - 100 ppm / kg. It was noted that corazole and caffeine in the tested doses cause a convulsive effect in all animals in the group. Preliminary administration of the test drug did not have an anticonvulsant effect, however, it slightly increased the time of onset of seizures. When studying the effect of this drug on the activity of the heart, it was found that it does not adversely affect the bioelectric activity of the heart.

Experiments to study the effect of the drug on the effect of sleeping pills were carried out on female white mice weighing 18-23 g. Sodium thiopental, sodium ethamine and chloral hydrate were used as sleeping pills. Derivatives of barbiturate acid (thiopental sodium and etyminal sodium) act mainly on subcortical formations, and chloral hydrate - on the cerebral cortex. During the experiments, it was found that the studied drug lengthens the duration of hypnotic action of sodium thiopental and sodium etaminal. The duration of sleep caused by chloral hydrate is somewhat shortened.

The drug in doses that cause a pronounced anti-inflammatory effect does not adversely affect the functions of various organs and systems.

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