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Synthesis of New Derivatives of Diphenyl Oxide

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Abstract—Studying of chemical properties of nitriles containing diphenyl oxide fragment in their structure opens wide prospects for obtaining new compounds possessing various chemical and pharmacological properties. They can be used as biologically active substances and ingredients of rubber mixtures of polyfunctional action. Effective synthetic approaches to imidate hydrochlorides, N-substituted imidates, and amidines containing 3-phenoxyphenyl fragment were developed from the corresponding nitriles like 3-(3-phenoxyphenyl)-2-propenylnitrile, 3-(3-phenoxyphenyl)-2-betenylnitrile, and 2-methyl-2-(3-phenoxybenzyloxy)propionitrile.

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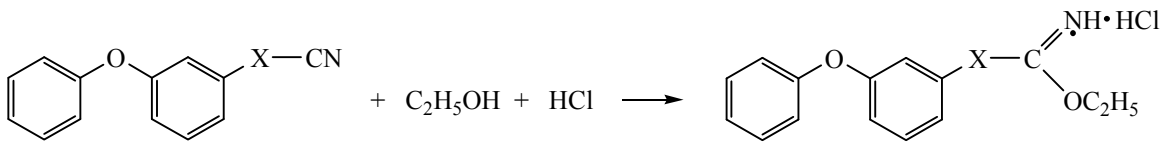
At present versatile types of pharmacological activity of the diphenyl oxide functional derivatives are well known. Thus, permethrin [(3-phenoxyphenyl)-methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropionate, a mixture of *cis*- and *trans*-isomers (3:1)] and phenothrin [(3-phenoxyphenyl)methyl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropionate] are used as drugs which possess antiparasitic, antipediculosis, insecticidal and ovicidal pharmacological actions [1, 2].

The use of phenoxyphenylacetylenes obtained on the base of 1-(2-methyl-4-phenoxyphenyl)ethanone and 1-(3-phenoxyphenyl)ethanone as antithrombotic, anti-inflammatory, antipyretic agents and analgesics is known [1].

Nitriles, imidate hydrochlorides, imidates, and amidines containing 3-phenoxyphenyl fragment are promising compounds for the synthesis of new psychotropic medicines and drugs acting on the protozoa organisms, viruses and atypical (tumorous) cells [3].

It is presumable that the elaboration of synthesis methods of imidate hydrochlorides containing 3-phenoxyphenyl fragment, N-substituted imidates and amidines would allow to obtain the new structures with various chemical and pharmacological properties.

Synthesis of ethylimidates hydrochlorides by the Pinner reaction. It is known from literature [4] that aliphatic, aromatic and heterocyclic nitriles react with alcohols and hydrogen chloride by Pinner reaction to give imidate hydrochlorides. The practical significance of imidate hydrochlorides is due to their solubility in water, an important property for using the biologically active compounds in practice. Nitriles containing diphenyl oxide fragment were found to react readily with ethanol and hydrogen chloride by Pinner reaction. We carried out hydrochlorination of nitriles by Pinner reaction to form the corresponding imidate hydrochlorides containing diphenyl oxide fragment:



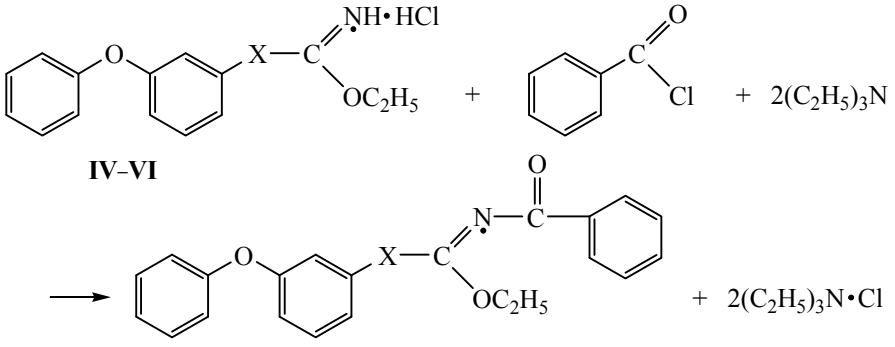
I–III **IV–VI**

X = —CH=CH— (**I, IV**); —C(CH3)=CH— (**II, V**); —C(=O)—O—C(CH3)2— (**III, VI**).

In all instances the reaction was carried out in the reagents bulk at 0–5°C at the equimolar ratio of nitrile, alcohol, and hydrogen chloride. The reaction completion was attested by the added weight of the reaction mixture. Gaseous hydrogen chloride for the synthesis of imidate hydrochlorides was obtained using sodium chloride of chemically pure grade, hydrochloric and sulfuric acids. Hydrogen chloride was dried by bubbling through concentrated sulfuric acid [4]. The structure and composition of the obtained imidate hydrochlorides were proved by the IR and ^{1}H NMR spectroscopy and elemental analysis data.

Synthesis of *N*-benzoyl-substituted ethylimidates containing diphenyl oxide fragment. *N*-Benzoyl-substituted imidates possessing hypoglycaemic, neuroleptic, tuberculostatic and fungicidal activities are very promising substances which may be used for the synthesis of the corresponding amidines.

We carried out reaction of imidate hydrochlorides containing diphenyl oxide fragment with benzoyl chloride according to the scheme:



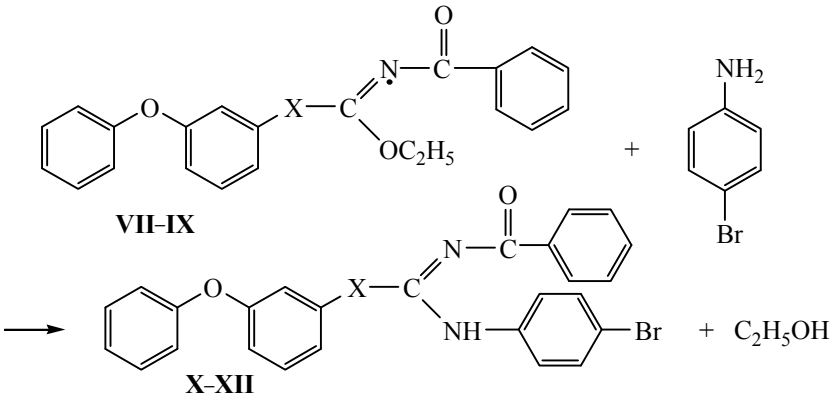
IV–VI **VII–IX**

X = —CH=CH— (**IV, VII**); —C(CH$_3$)=CH— (**V, VIII**); —C(=O)—O—C(CH$_3$)$_2$— (**VI, IX**).

Triethylamine was used as an acceptor of hydrogen chloride. This reaction was carried out at the equimolar ratio of reagents and twofold triethylamine excess in the anhydrous 1,4-dioxane at 60–65°C for 2 h. The product yields were 95–99%.

The structure and composition of the obtained *N*-benzoyl-substituted imidates were proved by the IR and ^{1}H NMR spectroscopy.

Synthesis of amidines containing diphenyl oxide fragment. The obtained *N*-benzoyl-substituted ethylimidates were involved into the reaction with *p*-bromoanilines:



VII–IX **X–XII**

X = —CH=CH— (**VII, X**); —C(CH$_3$)=CH— (**VIII, XI**); —C(=O)—O—C(CH$_3$)$_2$— (**IX, XII**).

The reactions were performed at 75–80°C in benzene over 2 h. The isolation of the N-substituted amidines by means of vacuum distillation leads to the target products in low yields. This process is accompanied with amidine decomposition. Under these conditions the yields do not exceeded 50%. Aiming to find more favorable method for the purification of the synthesized amidines, we performed TLC using the "Sorbfil" plates. As a result the conditions for products purifying by the column chromatography were found. The products yields amount to 95–99%. The structure and composition of the obtained *N*-benzoyl-substituted amidines were proved by the IR and ^{1}H NMR spectroscopy.

EXPERIMENTAL

The IR spectra were recorded in mineral oil using NaCl or KBr prisms on a Specord M-82 spectrophotometer. The ^{1}H NMR spectra were registered on a Varian Mercury 300BB instrument in DMSO-d_6, internal reference HMDS.

Hydrochloride of ethylimidate of 3-(3-phenoxyphenyl)-2-propenic acid (IV). A solution of 5.03 g (0.026 mol) of 3-(3-phenoxyphenyl)-2-propenylnitrile **I** and 1.26 g (0.027 mol) of anhydrous ethanol was placed into the weighed reactor. The reaction mixture was saturated with dry hydrogen chloride on cooling. The reaction completing is attested by increase in the reaction mass weight and its crystallization. Then the reaction mixture was kept overnight at 0–5°C, thereafter the hydrogen chloride excess was removed by evacuation. Yield 6.8 g (0.024 mol, 94%).

IR spectrum, ν, cm^{-1}: 1676 (C=C); 3064 (C–H); 1509 (NH^+); 1630 (C=N); 1240–1070 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.154 t (3H,CH_3); 4.207 m (2H, CH_2); 6.935–7.657 m (9H, $C_6H_5OC_6H_3$); 7.914 m (1H, NH); 7.46–7.48 d (1H, Ar-CH); 5.62–5.67 d (1H, CH–CN). Found, %: C 67.26, 67.24; H 5.90, 5.98; N 4.67, 4.70; Cl 11.71; 11.72. Calculated, %: C 67.22; H 5.93; N 4.61; Cl 11.7.

Hydrochloride of ethylimidate of 3-(3-phenoxyphenyl)-2-butenic acid (V) was prepared similarly. IR spectrum, ν, cm^{-1}: 1672 (C=C); 2930–3070 (C–H); 1486 (NH^+); 1638 (C=N); 970–1126 (C–O–C). ^{1}H NMR, δ, ppm: 1.150 t (3H, CH_3); 2.67 m (2H, CH_2); 6.622–7.657 m (9H, $C_6H_5OC_6H_3$); 7.64 m (1H,NH); 7.442–7.467 d (1H, CH–CN). Found, %: C 67.96, 68.04; H 6.29, 6.48; N 4.37, 4.40; Cl 11.17; 11.18. Calculated, %: C 68.03; H 6.30; N 4.41; Cl 11.18.

Hydrochloride of ethylimidate of 2-methyl-2-(3-phenoxybenzoyloxy)propenic acid (VI) was prepared similarly. IR spectrum, ν, cm^{-1}: 1654 (C=N); 2938 [ν(CH)]; 1287 [δ(CH_3)]; 1732 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.8 s (6H, CH_3); 1.2 t (3H, CH_3); 4.2 m (2H, CH_2); 6.9–7.8 m (9H, $C_6H_5OC_6H_4$); 9.0 m (1H, NH). Found, %: C 67.26, 67.24; H 5.90, 5.98; N 4.67, 4.70; Cl 11.71; 11.72. Calculated, %: C 67.22; H 5.93; N 4.61; Cl 11.7.

***N*-Benzoyl-substituted ethylimidate of 3-(3-phenoxyphenyl)-2-propenic acid (VII).** To a solution of 5.9 g (0.021 mol) of compound **IV** in anhydrous 1,4-dioxane were added dropwise in succession solutions of 4.25 g (0.042 mol) of triethylamine and 3 g (0.021 mol) of benzoyl chloride in 1,4-dioxane under stirring and cooling with ice bath. Then the reaction mixture was stirred for 30 min at room temperature and kept for 2 h at 60–65°C. The precipitated triethylamine hydrochloride was filtered off. The solvent was evaporated. Yield 6.8 g (0.02 mol, 95%). IR spectrum, ν, cm^{-1}: 1576 (C=C); 2900–3300 (C–H); 1695 (C=O); 1678 (C=N); 1240–1070 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.203 t (3H,CH_3); 4.207 m (2H, CH_2); 6.839–7.657 m (9H, $C_6H_5OC_6H_3$); 5.62-5.67 d (1H, CH–CN). Found, %: C 77.46, 77.60; H 5.60, 5.70; N 3.76, 3.80. Calculated, %: C 77.63; H 5.66; N 3.77.

***N*-Benzoyl-substituted ethylimidate of 3-(3-phenoxyphenyl)-2-butenic acid (VIII)** was prepared similarly. IR spectrum, ν, cm^{-1}: 1672 (C=C); 2930–3070 (C– H); 1678(C=O); 1678 (C=N); 970–1126 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.150 t (3H, CH_3); 2.67 m (2H, CH_2); 6.622–7.657 m (9H, $C_6H_5OC_6H_3$); 7.442–7.467 d (1H, CH-CN). Found, %: C 77.91, 77.92; H 5.93, 5.98; N 3.63, 3.68. Calculated, %: C 77.92; H 5.97; N 3.67.

***N*-Benzoyl-substituted ethylimidate of 2-methyl-2-(3-phenoxybenzoyloxy)propionic acid (IX)** was prepared similarly. IR spectrum, ν, cm^{-1}: 1654 (C=N); 2938 [ν(CH)]; 1287 [δ(CH_3)]; 1732 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.8 s (6H, CH_3); 1.2 t (3H, CH_3); 4.2 m (2H, CH_2); 6.9–7.8 m (9H, $C_6H_5OC_6H_4$); 9.0 m (1H, NH). Found, %: C 72.36, 72.38; H 5.80, 5.86; N 3.22, 3.30. Calculated, %: C 72.39; H 5.80; N 3.25.

***N*-Benzoyl-substituted amidine of 3-(3-phenoxyphenyl)-2-propenic acid (X).** To a solution of 4.8 g (0.014 mol) of compound **VII** in anhydrous benzene was added 1.23 g (0.017 mol) of *p*-bromoaniline under stirring and cooling with water bath. Then the reaction mixture was kept at 55–60°C for 2 h. The product was

isolated and purified by column chromatography eluting with a mixture diethyl ether : hexane (2:1). Yield 98% (0.137 mol), bp 252–254°C (4 mm Hg). IR spectrum, ν, cm^{-1}: 3320-3450 (C–N, N–H); 1740 (N–H); 1695 (C=O); 1678 (C=N); 1240-1070 (C-O-C). ^1H NMR spectrum, δ, ppm: 6.839–7.657 m (9H, $C_6H_5OC_6H_3$); 3.55 s (1H, NH); 7.44-7.46 d (1H, Ar-CH); 5.62–5.67 d (1H, CH–CN). Found, %: C 68.15, 68.22; H 4.18, 4.26; N 4.85, 4.88; Br 16.20, 16.24. Calculated, %: C 68.15; H 4.26; N 4.87; Br 16.23.

***N*-Benzoyl-substituted amidine of 3-(3-phenoxyphenyl)-2-butenic acid (XI)** was prepared similarly, bp 260–262°C (4 mm Hg). IR spectrum, ν, cm^{-1}: 3350–3500 (C–N, N–H); 1755 (N–H); 1708(C=O); 1672 (C=N); 970–1126 (C–O–C). ^1H NMR spectrum, δ, ppm: 6.622–7.657 m (9H, $C_6H_5OC_6H_3$); 7.442–7.467 s (1H, CH-CN); 3.55 s (1H, NH); 2.22–2.35 s (3H, CH_3). Found, %: C 68.61, 81.42; H 4.98, 5.00; N 6.28, 6.30; Br 15.78, 15, 81. Calculated, %: C 68.64; H 4.54; N 4.73; Br 15.78.

N-Benzoyl-substituted amidine of 2-methyl-2-(3-phenoxyenzoyloxy)propionic acid (XII) was prepared similarly, bp 258–260°C (4 mm Hg). IR spectrum, ν, cm^{-1}: 1654 (C=N); 2938 [ν(CH)]; 1287 [δ(CH_3)]; 1732 (C=O). ^1H NMR spectrum, δ, ppm: 1.8 s (6H, CH_3); 6.9–7.8 m (9H, $C_6H_5OC_6H_4$); 3.45 s (1H, NH). Found, %: C 65.06, 65.22; H 4.48, 4.53; N 5.00, 5.10; Br 14.41, 14, 45. Calculated, %: C 65.10; H 4.52; N 5.10; Br 14.47.

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