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SYNTHESIS OF NEW DERIVATIVES OF COLCHAMINE AND AMINOCOLHAMIN WITH PROPARGYL ESTER OF METHACRYLIC ACID

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ABSTRACT

Synthesized 4- (kolhaminoN-butyn-2-yl) ovine esters of methacrylic acid and 4- (aminocolhamino-N-butin-2-yl) ovine esters of methacrylic acid. The structures of the synthesized compounds were confirmed by IR and PMR data.

KEYWORDS: Kolhamin, aminocolhamine, propargyl, methacrylic acid.

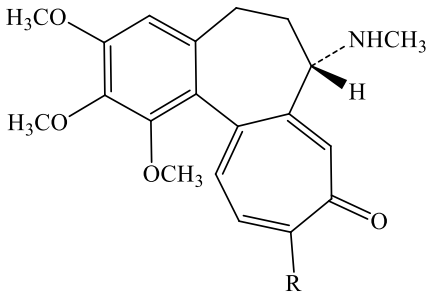
1. INTRODUCTION

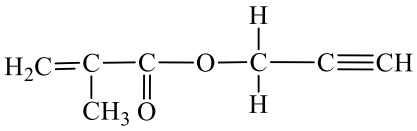
Recently, propargyl ethers have attracted attention due to a wide range of beneficial properties (propargyl ethers exhibit biological activity, contribute to the inhibition of corrosion and promote the flotation of rare metals, increase the energy intensity of complex rocket fuels). However, until now there are practically no generalized reviews in the literature on the methods of synthesis, physical, chemical, and applied properties of this class of heteroatomic acetylenes [1].

Among the numerous chemical compounds with antitumor activity, much attention is paid to tropolone alkaloids of lilac acids. In order to find less toxic compounds in this series, a large number of colchicine and colchamine derivatives have been synthesized.

It is known that the introduction into the molecule of drugs of groups containing the acetylene bond, significantly reduces their toxicity. Due to the fact that such work in the field of colchicine alkaloids has not previously been carried out, we synthesized colchamine derivatives with methacrylic acid propargyl ester (3) [2].

The starting compounds for the synthesis of derivative acetylenickolhamina (1) and aminokolhamina (2):





1.R=OCH_3
2.R=NH_2

The condensation reaction of colchamine with acetylene compounds was carried out according to Mannich [3], in equimolecular ratios of the reactants:

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The main starting compound, Kolhamin (1), for the syntheses carried out, was isolated from the Colchicum luteum baker growing in the Surkhandarin region.

2. MATERIALS AND METHODS

UV spectra were recorded on an SF-4A spectrometer in methanol, IR spectra were recorded on a UR-10 two-beam spectrometer in KBr, and the PMR spectra were measured on a Varian XL-100 instrument in $CDCl_3$.

a) Derivatives, kolhamina esters of organic acids. A portion of 1.0 g of colchamine was dissolved in 17 ml of dried and freshly distilled dioxane, and 0.12 g of para-form, 0.01 g of hydroquinone and 0.03 g of copper monochloride were added to the solution. After that, adding an equimolar amount of methacrylic acid propargyl ester to the solution, the contents of the flask were mixed well.
b) Derivatives of aminocolchaminos esters of organic acids. A weighed portion of 1.0 g of aminocolhamin was dissolved in 17 ml of dried and freshly distilled dioxane, and 0.12 g of para-form, 0.01 g of hydroquinone and 0.03 g of copper monochloride were added to the solution. After that, adding an equimolar amount of methacrylic acid propargyl ester to the solution, the contents of the flask were mixed well.

Table 1.Reaction conditions of methacrylic acid propargyl ester with kolhamin and aminokolhamin

№	Reagent	Estimatedamountof reagent	The amount of reagent taken	Productyield (%)
1.	Kolhamin	0,33	0,50	72
2.	Aminocolhamine	0,35	0,51	78

The reaction mixture was heated on a glycerin bath under reflux at 70-90 ° for 4-6 hours. The end of the reaction was determined by thin-layer chromatography of the reaction mixture.

After the practical completion of the reaction, insoluble substances in dioxane were separated by filtration and the solvent (dioxane) was distilled off on a rotary unit. The residue was dissolved in 20-30 ml of chloroform, the very dark chloroform solution obtained was extracted three times with 20 ml of 5% acetic acid.

The acetic extract contains unreacted kolhamin, which is isolated by alkalizing an acidic solution with ammonia and extraction with chloroform.

The chloroform solution of the reaction product, after separating the starting colchamine, was dried over anhydrous sodium sulfate, the sulfate was filtered, and the filtrate was passed through a small layer (5-7 g) of alumina. At the same time, the dark extract is strongly clarified. The solvent was distilled off and the reaction product was dried in a vacuum desiccator.

The final reaction products are obtained in the form of non-crystalline light yellow powders.

3. RESULTS AND DISCUSSION

As a result, we synthesized; 4- (kolhaminoN-butin-2-yl) methacrylic esters of methacrylic (4) aminocholamine-4- (aminocholamino-N-butyn-2-yl) methacrylic esters of methacrylic (5) (Table 2) [4].

During the hydrolysis of esters 4, 4- (colchamino-n-butin-2-yl) alcohol 6 is formed.
The compounds obtained are light yellow colored powders, about close to each other values of R_f. At the same time, by chromatographic mobility they are very different from the original collamide and aminocolhamin, having high R_f values.

The structures of the synthesized compounds were confirmed by IR and PMR data. In the IR spectra of compounds with an ester group (3-4), absorption bands of the carbonyl group (1735-1730 cm^{-1}) appear.
The Kolchamin and Aminocolchamin Fragments of the synthesized compounds do not differ significantly in the PMR spectra: the signals of the N-methyl group appear at 2.20-2.22 ppm of methoxyl groups - 3.56-3.60 (at C-

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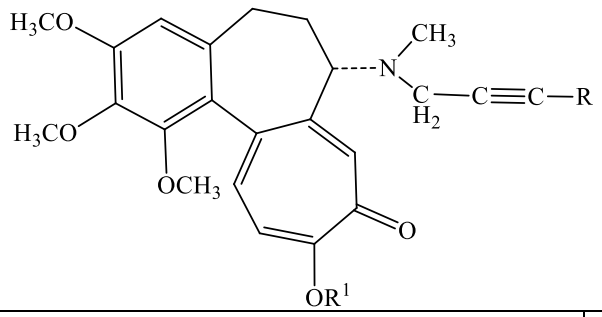
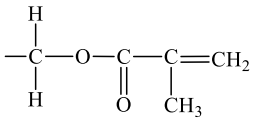
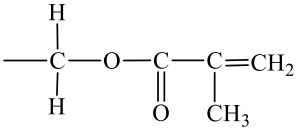
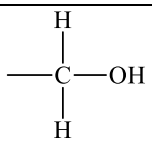
1) and 3 , 82-3.85 ppm (at C-2, C-3 C-10), proton H-4 - at 6.44-6.51 ppm, H-8 - 7.90-7.96 ppm, H- 11 - 6.68-6.75 ppm and H-12, 7.17-7.22 ppm.

Table 2. Synthesized acetylenic derivatives



R	R^1
 4.	OCH_3
 5.	NH_2
 6.	OCH_3

Characteristic of all acetylenic derivatives is the presence in their PMR spectra of a two-proton doublet from the bridging N-CH2 group, which manifests itself in the region of 3.32-3.38 ppm. The bridge OCH_3 group present in compounds 4–5 forms a narrow two-proton doublet in the region of 4.53–4.70 ppm.

The signals of C-alkyl groups appear in the strongest spectral field (1.4-2.0 ppm) and are easily decoded. Olefinic protons of methacrylic esters resonate at 5.98 ppm. (cis-) and 3.48 ppm (trans-protons). The most complex spectra of colchamine and aminocolchamin with propargyl ester are methacrylic acid propargyl ester, in which the signals of the protons of two benzene rings overlap.

4- (colchamino N-butyn-2-yl) methacrylic ester esters (4).
IR spectrum: 1090, 1250, 1480, 1570, 1590, 1655, 1730, 2225, 2800, 2840, 2935, 2950, 3500 cm^{-1}.
^{1} H NMR spectrum: 2.20 (3H, s, N-CH_3), 3.34 (N-CH_2), 3.58 (3H.s., -OCH_3), 3.82; 3.84; 3.85 (3H x 3, ss, 3OCH_3), 3.96 (OH_3), 4.70 (OCH_2), 6.48 (H-4), 7.38-7.56 (H-4, H- 11, $H_{\beta,\ \beta,\ \gamma}$, phenyl radical), 7.80-8.00 (H-8, H-12, Hα, α-phenyl radical), 8.16 (methane proton, hemanal to cyan group) ppm.

Due to the alkyl (and not acyl) nature of the substituents introduced into the amino group, the derivatives obtained retain to some extent basicity (especially with the pyridine ring), which makes it difficult to separate the colchamine impurity from the reaction products. Therefore, for this purpose, the method of chromatography on alumina (eluents mixture of ether-acetone, acetone and acetone-methanol) was used.

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4- (aminocolchamino-N-butyn-2-yl) methacrylic acid esters (5).
IR spectrum: 1100, 1170, 1720, 2570, 2950, 3400, 3540 cm^{-1}.

HMR spectrum: 1.26; 1.45; 1.49 (CH_3CH_2), 1.98 (CH3). 2.16 (N-CH_3), 3.58; 3.85 x 2, 3.88 (3H x 4, ss, 4 OCH_3), 5.16 (OH), 6.48 (H-4), 6.94 (H-11), 7.24 (H –I2 and H-8) ppm

4. CONCLUSION

- Synthesized derivatives of kolhamine and aminocolhamin with propargyl ester of methacrylic acid.
- The structures of the synthesized compounds were confirmed by IR and PMR spectra.

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