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SYNTHESIS OF A NEW DERIVATIVE OF COLKHAMINE WITH DIMETHYLETHYNYLCARBINOL

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Abstract:4-(Kalamin N/1,1-dimethylbutyn-2) carbinol has been synthesized. The structure of the synthesized compound was confirmed by IR and NMR spectral data.

Keywords: Colchamine, dimethylethynylcarbinol, 4-(colchamine N/1,1-dimethylbutyn-2) carbinol.

Introduction

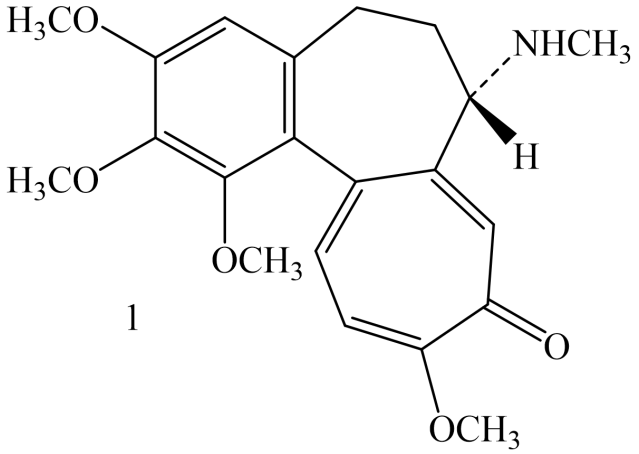
Colchamine is the second most common tropolone alkaloid in colchicum plants, following colchicine in prevalence and content. Colchamine differs from colchicine in having a more pronounced basicity, which is utilized for their separation.

The structure and chemical transformations of colchamine have been primarily studied by Kiselev and Shantavy along with their colleagues. Colchamine is 7-8 times less toxic than colchicine.

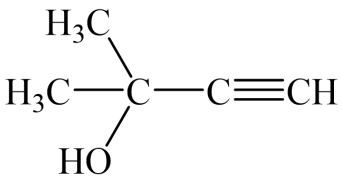
It is known that introducing groups containing an acetylene bond into the molecules of pharmaceutical compounds significantly reduces their toxicity. Since no prior research in the field of colchicine alkaloids has been conducted in this direction, we have synthesized colchamine derivatives (1) with dimethylethynylcarbinol (2).

Literature review and methodology

Starting compounds for the synthesis of acetylene derivatives of colchamine (1):



1



2

The condensation reaction of colchamine with acetylene compounds was carried out according to the Mannich reaction in equimolar ratios of the reagents. The main starting compound, colchamine (1), used for the synthesis, was extracted from Colchicum luteum Baker growing in the Surkhandarya region.

As a result, we synthesized 4-(colchamine N/1,1-dimethylbutyn-2) carbinol (3).

The obtained compounds are light yellow powders with similar Rf values. However, their chromatographic mobility differs significantly from the initial colchamine, exhibiting high Rf values.

A characteristic feature of all acetylene derivatives is the presence of a two-proton doublet from the bridging N-CH_2 group in their NMR spectra, appearing in the range of 3.32–3.38 ppm. The

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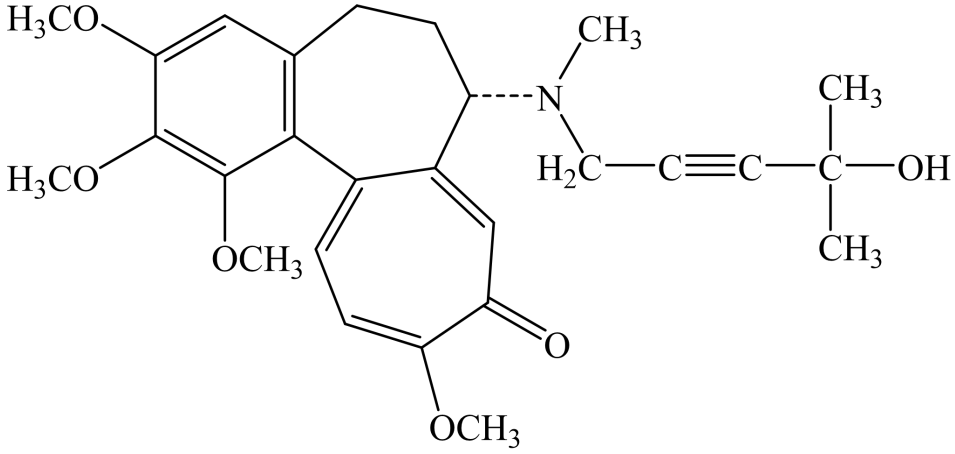
bridging OCH_3 group, present in compounds 4–5, forms a narrow two-proton doublet in the range of 4.53–4.70 ppm.

The structure of the synthesized compounds was confirmed by IR and NMR spectral data. In the IR spectra of compounds containing an ester functional group (3–4), absorption bands of the carbonyl group appear at 1735–1730 cm^{-1}.

The colchamine fragments of the synthesized compounds show no significant differences in their ^1H NMR spectra:

- The N-methyl group signals appear at 2.20–2.22 ppm.
- The methoxy groups resonate at 3.56–3.60 ppm (at C-1) and 3.82–3.85 ppm (at C-2, C-3, and C-10).
- The proton at H-4 appears at 6.44–6.51 ppm, H-8 at 7.90–7.96 ppm, H-11 at 6.68–6.75 ppm, and H-12 at 7.17–7.22 ppm.

The synthesized acetylene derivative... (incomplete sentence—please clarify if you need further elaboration).



Experimental section

a) Derivatives of Colchamine with Methyl ethyl ethynyl Carbinol

A sample of 1.0 g of colchamine was dissolved in 17 mL of dried and freshly distilled dioxane, and 0.12 g of paraform, 0.01 g of hydroquinone, and 0.03 g of zinc chloride were added to the solution. After that, an equimolecular amount of dimethylethynylcarbinol was added to the solution, and the contents of the flask were thoroughly mixed.

Table 1

Reaction conditions of dimethylethynylcarbinol with colchamine

№		Calculated Amount of Reagent	Taken Amount of Reagent	Product yield (%)
1	Colchamine	0.78	1.0	96

The reaction mixture was heated in a glycerin bath under reflux at 80-100°C for 6-8 hours. The reaction completion was monitored using thin-layer chromatography of the reaction mixture. After the reaction was practically complete, insoluble substances in dioxane were separated by filtration, and the solvent (dioxane) was removed using a rotary evaporator.

The residue was dissolved in 20-30 mL of chloroform, and the resulting dark chloroform solution was extracted three times with 20 mL of 5% acetic acid. The acetic acid extract contained unreacted colchamine, which was isolated by alkalizing the acidic solution with ammonia and extracting with chloroform.

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The chloroform solution of the reaction product, after separating the initial colchamine, was dried over anhydrous sodium sulfate. The sulfate was filtered off, and the filtrate was passed through a small layer (5-7 g) of aluminum oxide, which significantly lightened the dark extract. The solvent was then evaporated, and the reaction product was dried in a vacuum desiccator.

The final reaction products were obtained as non-crystalline, light yellow powders.

4-(Colchamine N/1,1-dimethylbutyn-2) carbinol (3)

IR spectrum (cm^{-1}): 1100, 1170, 1720, 2570, 2950, 3400, 3540

^1H NMR spectrum (δ, ppm):

1.26, 1.45, 1.49 (CH_3CH_2)

1.98 (CH_3)

2.16 (N-CH_3)

3.58; 3.85 ×2, 3.88 (3H × 4, s, 4OCH_3)

5.16 (OH)

6.48 (H-4)

6.94 (H-11)

7.24 (H-12 and H-8)

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