MEDICINAL PLANTS

FRAGMENTATION OF NITRO(BROMO)-SUBSTITUTED METHYLPAPAVERINIUM IODIDES UNDER KOST – SAGITULLIN REACTION CONDITIONS

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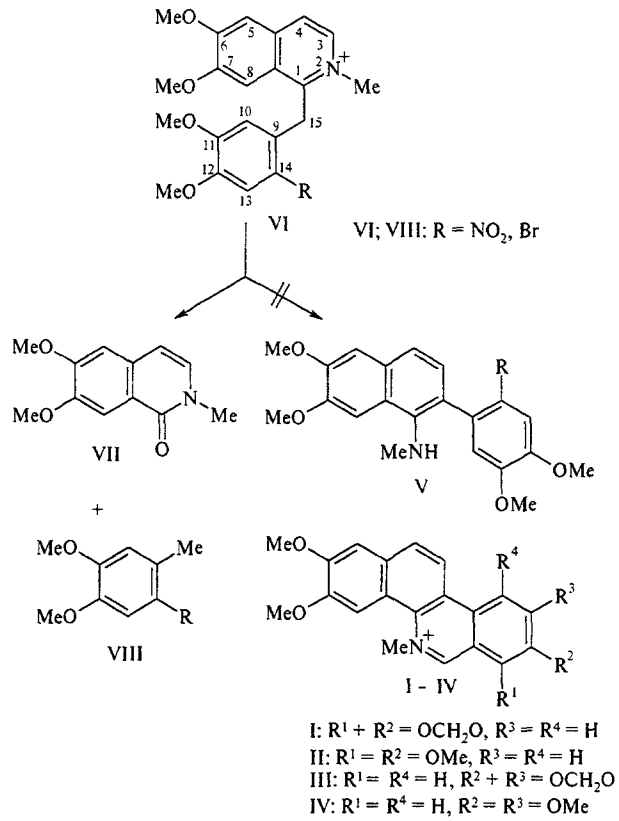
Benzo[c]phenanthridine alkaloids such as sanguinarine (I), chelerythrine (II), nitidine (III), and avicine (IV), as well as some other compounds of this series, draw considerable interest of researchers because of their broad spectrum of biological and pharmacological activity [1]. In particular, compounds I and II exhibited high antibacterial activity [2], while compounds III and IV showed pronounced antitumor properties [3 – 5]. In order to expand the stock of raw materials for the production of related drugs, synthetic approaches to preparation of the above alkaloids and their analogs have been developed [6 – 8]. According to a scheme proposed by Suvorov et al. [9 – 11], the key compounds in the synthesis of benzo[c]phenanthridine derivatives are 3-aryl-2-aminonaphthalene derivatives of type V; these compounds are usually obtained via the corresponding dihydro and tetrahydro derivatives [12]. A possible approach to the synthesis of these compounds consists of the isomerization recyclization (known as the Kost – Sagitullin rearrangement) of papaverine derivatives (VI, R = H) proceeding via the stage of heterocyclic ring opening [13 – 16].

In this reaction, a methoxy group in position 6, conjugated to a tertiary nitrogen atom of the isoquinolone nucleus, is replaced by a methylamino group, provided that the rearrangement is performed in the presence of methylamine base [17, 18]. The use of methylamine acetate suppresses the substitution of the methylamino group for the 6-methoxy group, but leads to a low yield of the target compound V (5%), explained by insufficient CH-acidity of the benzyl methylene group. In order to study the effect of various substituents on this reaction, we have used bases with electron-acceptor substituents in the aromatic ring of the benzyl fragment. We have established that this leads, instead of to the rearrangement mentioned above, to the fragmentation of 14-R-papaverine methyl iodides VI ($R = NO_2$, Br) with the formation of 6,7-dimethoxy-2-methyl-1,2-dihydroisoquinol-1-one (VII) and the corresponding substituted 3,4-dimethoxytoluenes (VIII).[2]



It was demonstrated [19] that compound VI ($R = NO_2$) exhibits analogous fragmentation under alkaline conditions (boiling with 33% KOH). Dihydroisoquinolone VII and the

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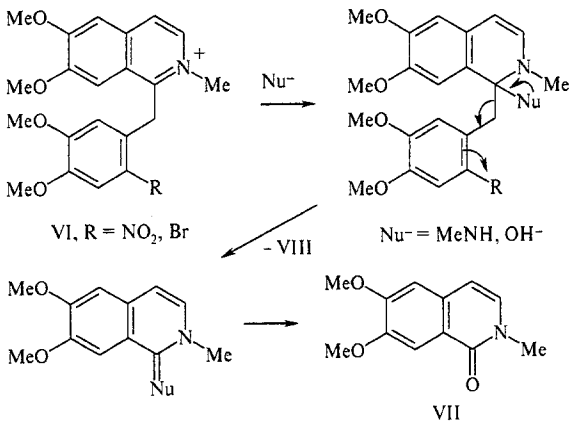
[2] In the papers cited above, compounds VI are referred to as 6'-R-papaverine methyl iodides.

corresponding veratric acid derivative were also obtained by oxidation of compounds VI (R = NO_2, Br) with potassium permanganate [19, 20] and by photochemical oxidation of compound VI (R = Br) by oxygen from air under alkaline conditions. Thus, the use of substituted papaverines VI for the synthesis of compounds V containing electron-acceptor substituents (B = NO_2, Br) is a low-efficiency pathway. We may suggest that the mechanism of fragmentation of compounds VI includes nucleophilic addition at the bond 1 – 2, followed by rupture of bond 1 – 15:



Isoquinolone VII is a natural compound isolated from *Thalictrum alpinum L.* [21].

EXPERIMENTAL PART

The course of the reactions was monitored and the purity of the reaction products was checked by TLC on Silufol UV-254 plates eluted in a chloroform – methanol – 25% aqueous NH_4OH system (45 : 5 : 0.2). The mass spectra were obtained with a Varian MAT CH8 spectrometer operated at an electron impact ionization energy of 70 eV. The ^1H NMR spectra were measured on a Gemini 200 spectrometer (Varian, USA) operated at a working frequency of 200 MHz, using $CDCl_3$ as the solvent and TMS as the internal standard.

14-Nitro-N-methylpapaverinium iodide VI (R = NO_2) was synthesized by the original method described in [19].

14-Nitro-N-methylpapaverinium iodide VI (R = Br) was synthesized as described in [20].

Reaction between 4-nitro-1-methylpapaverinium iodide and methylamine acetate. A mixture of 0.34 g of iodide VI (R = NO_2) and 2.5 g methylamine acetate in methanol was heated for 3 days at 100°C in a sealed ampule. Then the ampule was opened and the mixture poured into a 5% sodium carbonate solution. The products were extracted with chloroform and the extract was concentrated in vacuum. The residue was chromatographed on a silica gel column eluted with a chloroform – methanol mixture to obtain 0.075 g of nitrohomoveratrole VIII (R = NO_2) and 0.031 g of isoquinolone VII.

1-Methyl-2-nitro-4,5-dimethoxybenzene VIII (R = NO_2): m.p., 120°C (reported m.p., 118 – 120 [19]); mass spectrum (m/z; I_{rel}, %): M+ 197 (85), 180 (100), 152 (70).

N-Methyl-6,7-dimethoxy-1,2-dihydroisoquinolin-1-one VII: m.p., 111 – 112°C (reported m.p., 112 – 113 °C [21]); ^1H NMR spectrum (δ, ppm): 3.60 (s, 3H, NMe), 3.99 (s, 3H, 7-OMe), 4.01 (s, 3H, 6-OMe), 6.40 (d, 1H, J 9 Hz, 4-H), 6.85 (s, 1H, 8-H), 7.00 (d, 1H, J 9 Hz, 3-H), 7.80 (s, 1H, 5-H); mass spectrum m/z (I_{rel}, %): M^+ 219 (90), 204 (65), 188 (100), 176 (100).

Similar procedure was used for the reaction between 14-bromo-N-methylpapaverinium iodide VI (R = Br) and methylamine acetate; here, the reaction products exhibit considerable gumming. A compound isolated from the reaction mixture was identified as N-methyl-6,7-dimethoxy-1,2-dihydroisoquinolin-1-one (VII) by data of TLC and mass spectrometry.

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