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SYNTHESIS OF BUTOXYBUTENYNE BASES AND THEIR QUATERNARY SALTS AND INVESTIGATION OF THEIR PHARMACOLOGICAL PROPERTIES

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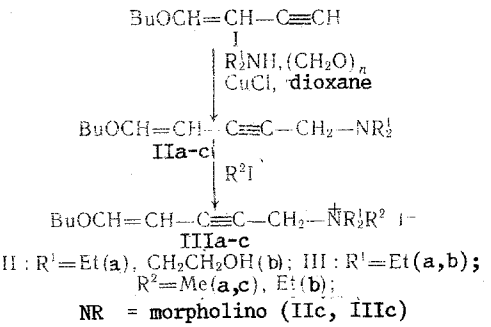
Acetylenic Mannich bases have a wide spectrum of pharmacological activity (see [1]), but only a few of them have been tested for their antitumorigenic activity, in particular, the Mannich bases obtained from propargyl ethers.

To study the antitumorigenic activity, we synthesized Mannich bases (IIa-c) obtained from 1-butoxy-but-1-en-3-yne [1], which is the main component of the flotation agent MIG-4. Methoxybutenyne Mannich bases are described in the literature, but their pharmacological properties have not been investigated [5].

Acetylenic amines II were synthesized under the conditions of a catalytic Mannich reaction, similar to those described in [5]. The quaternary salts III were obtained by quaternization of amines II with methyl or ethyl iodide in an acetonitrile medium. The structure of compounds II and III was confirmed by IR and PMR spectra.



EXPERIMENTAL (CHEMICAL)

The IR spectra were run on "UR-20" and "Specord" spectrophotometers, the PMR spectra — on a "Tesla BS-467" spectrometer (60 MHz), of amines (II) in CCl_4, of salts III in deuteroacetone, using TMS as internal standard. The characteristics of the synthesized compounds are given in Table 1. The results of the elemental analyses correspond to the calculated values.

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Yield, %	Bp °C/mm Hg (mp, °C)	Empirical formula
IIa	72	100 °C/1 mm	$C_{13}H_{23}NO$
IIb	63	Liquid, not distillable in vacuo	$C_{13}H_{23}NO_3$
IIc	55	116 °C/1 mm	$C_{13}H_{21}NO_2$
IIIa	70	(61—2 °C)	$C_{14}H_{26}NIO$
IIIb	80	(78—9 °C)	$C_{15}H_{28}NIO$
IIIc	65	(45—6 °C)	$C_{14}H_{24}NIO_2$

TABLE 2. Biological Properties of Synthesized Compounds

Compound	Dose, mg.kg	Number of administrations	It, %	Kp, %	"	LD_{50}, mg/kg
IIa	20	6	26	+13	>0,9	115
IIb	20	6	16	+2	>0,9	120
IIc	25	7	27	10	>0,95	135
IIIa	30	7	22	6	>0,95	164
IIIb	30	6	31	8	>0,99	172
IIIc	35	6	35	6	>0,99	183

5-Butoxypent-4-en-2-ynyldialkylamines (IIa-c). A 3 g portion (0.1 mole) of paraform and 0.1 g of cuprous chloride were added to a mixture of 12.42 g (14.5 ml, 0.1 mole) of 1-butoxybut-1-en-3-yne [1], 0.1 mole of the corresponding secondary amine and 50 ml of dry dioxane, and the mixture was boiled under a reflux condenser for 2 h in an argon atmosphere. After cooling, the reaction mixture was diluted with 300 ml of water with addition of 30 ml of glacial AcOH and the impurities insoluble in aqueous AcOH were extracted with ether. For the isolation of amines IIa, c, the aqueous layer was made alkaline by the addition of K_2CO_3 to pH 9-10, and the amine II that separated out was extracted with ether (3 × 50 ml). The extract was dried over K_2CO_3, the ether was evaporated, and the product was distilled under vacuum. For the isolation of amine IIb, the aqueous layer was saturated with K_2CO_3 and extracted with ether (3 × 100 ml). The extract was dried over K_2CO_3 and purified from resinous impurities by passing through a short (5 cm) column with silica gel. After the evaporation of ether (the last portions under water-jet pump vacuum), a pure amine IIb was obtained. The IR spectra of amines II are characterized by strong bands at 1630 cm^{-1} of the olefinic bond and at 1270 cm^{-1} of the vinyl ether group, and also by a weak band of the acetylenic bond at 2220 cm^{-1}.

5-Butoxypent-4-en-3-ynyltrialkylammonium iodides (IIIa-c). A 0.015 mole portion of alkyl iodide was added to a solution of 0.01 mole of the corresponding amine II in 20 ml of dry acetonitrile, and the mixture was boiled for 2 h on a water bath under a reflux condenser. It was then cooled and the quaternary salt III was precipitated by the addition of 150 ml of ether. Salts III precipitate in the form of oils which solidify on standing.

EXPERIMENTAL (PHARMACOLOGICAL)

The tests of the acute toxicity and antitumorigenic action of Mannich bases IIa-c and their quaternary salts IIIa-c were carried out on white nonpedigree mice and rats of both sexes each weighing 18-20 and 110-120 g, respectively.

The compounds were tested in the form of finely dispersed suspensions prepared ex tempore in a 10% solution of polyvinylpyrrolidone.

The toxicity of the compounds was studied on nonpedigree mice with a single intraperitoneal administration. For each compound, a dose causing the death of one half of the animals in a group (LD_{50}) was determined.

The antitumorigenic activity of the compounds was determined on nonpedigree rats with Jensen sarcoma transplanted under the skin. The compounds were administered to the animals intraperitoneally, daily, for 6-7 days, beginning the therapy from the 5-th day after the transplantation of the tumor (in doses of 1/4-1/6 LD_{50}). The therapeutic effect was

evaluated from the percent of inhibition of the tumor growth (It, %). The tolerability of the compounds was determined from the growth coefficient of the animals (Kp, %) [3]. The data obtained were subjected to a statistical treatment according to the Student-Fischer method [2].

In the investigation of the acute acidity it was found that all the compounds have moderate toxicity; their LD_{50} during intraperitoneal administration is 115-183 mg/kg (Table 2).

The study of the antitumorigenic activity of the butoxybutenyne derivatives did not reveal among them compounds displaying a pronounced activity with the absence of a toxic effect. Iodides IIIb, c exhibited the highest antitumorigenic activity. Thus, compound IIIb inhibited the growth of the Jensen sarcoma by 31%, and compound IIIc – by 35%. Compound IIc was less active (It - 27%). The therapeutic effect of compounds IIb and IIa was lower than the minimal activity criterion for a strain of Jensen sarcoma [4]. Compound IIa caused a stimulation of tumor growth (It = –26%).

It was thus shown that among the described butoxybutenyne Mannich bases and also among their quaternary salts, compounds displaying an antitumorigenic activity in tests in vivo are to be found. However, the level of this activity is insufficiently high.

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STUDY OF THIOAMIDES AND THEIR DERIVATIVES.

XII. CERTAIN REACTIONS OF 1-[α-METHYLTHIO-(p-TRIMETHYLAMMONIA)-BENZYLIDENE]PIPERIDINIUM SALTS

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The possibility of conversion of 1-(p-dialkylamino)thiobenzoylpiperidine into both 1-[α-alkylthio(p-dialkylamino)benzylidene]piperidinium (III, IV) salts and into 1-[α-alkylthio(p-dialkylammonia)benzylidene]piperidinium salts (I, II), shown in the preceding paper [1] prompted the author of the present paper to undertake the investigation of reactions of these compounds with certain hydrazine derivatives. It was assumed that compounds with potential cytostatic properties might thus be obtained.

The substrates in the reactions carried out were 1-[α-methylthio-(p-trimethylammonia)-benzylidene]piperidinium bromide and iodide (I, II), which were subjected to the action of thiosemicarbazide, isonicotonic acid hydrazide and picolinic acid amidrazone.

The condensation was carried out at room temperature and at the boiling point of the solvent (ethanol or pyridine). The reactions carried out are illustrated below. The structure of the new compounds, obtained in the present work, was confirmed by the elemental and spectral analyses. For 3-(p-trimethylammonia)-phenyl-5-methylthio-1,2,4-triazole bromide (VII) a mass spectral analysis was also carried out.

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