Trans-3-ethyl-2,3,4α,9,10,10α-hexahydro-4H-naphth[2,1-b]-1,4-oxazine (If) was obtained from IV and 10.68 g of IIIf, 1 h at 100°C. A 100-ml portion of water was added to the reaction mixture and IIf was extracted with ether. The extract was dried and evaporated. A 17.5-g portion of 60% H_2SO_4 was added to the residue (14 g). Yield 2.05 g (16%). bp 100-106°C/3 mm. IR spectrum, ν_{max}, liquid: 750 (1,2-disubstituted benzene ring), 1100 (C—O—C), 3330 cm^{-1} (NH). Hydrochloride. $C_{14}H_{20}ClNO$, mp 241-245°C (ethanol—ether).

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CHOLINOLYTIC ACTIVITY OF PIPERIDINOBUTINE ESTERS OF CERTAIN CARBOXYLIC ACIDS

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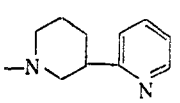
The well-known muscarine choline receptor antagonists (M-CR) constitute analogs of agonists that incorporate large hydrophobic radicals, i.e., the antagonists are "weighted" analogs of the agonists [1]. The muscarine antagonists apparently interact not only at the active center (recognition center) of the M-CR, but outside it as well. A well-known muscarine agonist is (acetoxy-2-inyl)trimethylammonium (IP-59) [2]. In our own work we investigated the muscarinolytic activity of its "weighted" analogs, namely the piperidino- and anabasinobutine esters of acetic, thioacetic, and thiobenzoic acids. The indicated acetic acid derivatives were obtained by the following synthesis pattern:

$$HOCH_2C{\equiv}CH \xrightarrow{CH_2O,\ HR} \underset{\text{I, II}}{HOCH_2C{\equiv}CCH_2R} \rightarrow$$

$$\rightarrow \underset{\text{III, IV}}{CH_3C(O)OCH_2C{\equiv}CCH_2R},$$

where R - N-piperidyl (I, III) or


(II, IV)

We synthesized 4-hydroxybutinylpiperidine (I) and 4-hydroxybutinylanabasine (II) by the aminomethylation of propargylic alcohol in the presence of catalytic quantities of CuCl. When these synthesized compounds were reacted with acetyl bromide in the presence of triethylamine they formed N-(4-acetoxybut-2-inyl)piperidine (III) and N-(4-acetoxybuty-2-inyl)-anabasine (IV).

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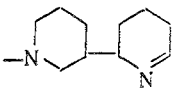
Analogous piperidine and anabasine derivatives of thioacetic and thiobenzoic acids were obtained by the following synthesis pattern:

$$RC(O)SK \xrightarrow{BrCH_2C\equiv CH} RC(O)SCH_2C\equiv CH \xrightarrow{CH_2O,\ HR^1} RC(O)SCH_2C\equiv CCH_2R^1$$

V—VII

where R=CH_3, (V, VI), C_6H_5 (VII);
R^1 = N-piperidyl (V, VII),


(VI)

By reacting propargyl bromide with potassium thioacetate or thiobenzoate we synthesized the corresponding S-propargylthioacetate or benzoate which were converted by aminomethylation in the presence of CuCl to N-(4-acetylmercaptobut-2-inyl)piperidine (V), N-(4-acetylmercaptobut-2-inyl)anabasine (VI), and N-(4-benzoylmercaptobut-2-inyl)piperidine (VII).

The corresponding iodomethylates were obtained by reacting III-VII with methyl iodide in ether at room temperature.

EXPERIMENTAL (CHEMICAL)

N-(4-Hydroxybut-3-inyl)anabasine (II). A mixture of 16.2 g (0.1 mole) of anabasine, 4.5 g (0.15 mole) of paraform, 5.6 g (0.1 mole) of propargylic alcohol, and 1 g (0.15 mole) of CuCl was boiled for 5 h in 100 ml of dioxane. A 100-ml portion of water was added to the cooled mixture and the pH of the solution was brought up to 3 by the addition of 5 N HCl and extracted with ether. The organic part was separated and a saturated $NaHCO_3$ solution was added to the inorganic part to bring the pH to 7, followed by extraction with ether 3 × 50 ml. After the extract was dried over Na_2SO_4 the ether was evaporated and the residue was extracted with hexane 3 × 20 ml. The hexane was then evaporated to yield 19.8 g (90%) of II which was a light yellow oil with n_D^{20} 1.5460 $C_{14}H_{18}ON_2$. The element analysis data for II and the compounds enumerated subsequently satisfied the calculated values.

N-(4-Hydroxybut-2-inyl)piperidine (I) was obtained in the same manner as compound II. Yield 91%, bp 107°C/1 mm, n_D^{20} 1.5062. $C_9H_{15}NO$.

N-(4-Acetoxybut-2-inyl)piperidine (III). A mixture of 2.12 g (0.021 mole) of triethylamine and 3.06 g (0.02 mole) of I in 20 ml of ether was added to 2.46 g (0.02 mole) of acetyl bromide in 50 ml of ether at 0°C. The mixture was stirred for 1 h at 0°C and 1 h at 20°C. The precipitate was filtered off and the solvent evaporated. The residue was vacuum-distilled to yield 3.2 g (80%) of III, bp 105°C/2 mm $[d]_4^{20}$ 1.0209, n_D^{20} 1.4825. $C_{11}H_{17}NO_2$.

N-(4-Acetoxybut-2-inyl)anabasine (IV). A mixture of 1.11 g (0.011 mole) of triethylamine and 1.53 g (0.01 mole) of I in 20 ml of ether was added to 1.23 g (0.01 mole) of acetyl bromide in 50 ml of absolute ether at 0°C. After 1 h the temperature of the reaction mixture was raised to room temperature. After 2 h the precipitate was filtered off, the solvent evaporated, and the residue was purified on a silica gel 100/160 chromatography column (eluent benzene—acetone, 4:1) to yield 1.9 g (75%) of IV, n_D^{20} 1.0855, n_D^{20} 1.5255. $C_{16}H_{20}N_2O_2$.

S-Propargylthioacetate. A 3.75-g portion (0.05 mole) of propargyl chloride at 20°C was added to 5.7 g (0.05 mole) of potassium thioacetate in 100 ml of alcohol. The reaction mixture was then boiled for 2 h, the precipitate filtered off, the solvent evaporated, and the residue was distilled to yield 4.5 g (80%) of S-propargylthioacetate, bp 55°C/12 mm, $[d]_4^{20}$ 1.0696, n_D^{20} 1.5020. C_5H_6OS.

N-(4-Acetylmercaptobut-2-inyl)piperidine (V). A mixture of 2.28 g (0.02 mole) of S-propargylthioacetate, 1.7 g (0.02 mole) of piperidine, 1 g (0.033 mole) of paraform, and 0.15 M of CuCl in 50 ml of dioxane was boiled for 5 h. A 50-ml portion of water was added to the cooled mixture to bring the pH to 3. The organic portion was separated and the pH of the aqueous portion was brought up to 7 by the addition of a saturated $NaHCO_3$ solution. The ether extract 3 × 50 ml was dried over Na_2SO_4, then evaporated, and the residue was purified on a silica gel L 40/100 column (eluent hexane—acetone, 9:1) to yield 3.3 g (77%) of V, $[d]_4^{20}$ 1.0510, n_D^{20} 1.5266. $C_{11}H_{17}NOS$.

TABLE 1. Iodomethylates of Aminobutine Esters of Acetic, Thioacetic, and Thiobenzoic Acids

Compound	Yield, %	mp, °C	Empirical formula
III·HI	90	Light yellow glass	$C_{12}H_{20}INO_2$
IV·HI	91	172—4	$C_{17}H_{23}IN_2O_2$
V·HI	87	Light yellow glass	$C_{12}H_{20}INOS$
VI·HI	88	222—4	$C_{17}H_{23}IN_2OS$
VII·HI	85	250 with decomposition	$C_{17}H_{22}INOS$

TABLE 2. Muscarinolytic Activity (K_D, M) of Compounds III-VII on the Axial Muscle of the Rat Ileum

Compound	K_D, M
III	Inactive $(2\cdot10^{-5})$
IV	Inactive $(2\cdot10^{-5})$
V	Inactive $(2\cdot10^{-5})$
VI	$1{,}0+0{,}2\cdot10^{-7}$ (4)*
VII	Inactive $(2\cdot10^{-5})$
III·HI	Inactive $(2\cdot10^{-5})$
IV·HI	$1{,}4+0{,}3\cdot10^{-5}$ (4)
V·HI	$1{,}5+0{,}3\cdot10^{-5}$ (3)
VI·HI	$3{,}3+0{,}5\cdot10^{-6}$ (4)
VII·HI	$1{,}2+0{,}3\cdot10^{-7}$ (4)
IP-59 †	$7{,}0+1.5\cdot10^{-7}$ (5)

*Number of experiments in parentheses.
†EC_{50} value given.

N-(4-Acetylmercaptobut-2-inyl)anabasine (VI) was obtained in the same manner as compound V to yield 72%, $[d]_4^{20}$ 1.1132, n_D^{20} 1.1132. $C_{16}H_{20}N_2OS$.

S-Propargylthiobenzoate. A 11.9-g (0.1 mole) portion of propargyl bromide at 20°C was added to 12.8 g (0.1 mole) of potassium thiobenzoate in 200 ml of alcohol. The reaction mixture was boiled for 2 h and the precipitate was filtered off. The solvent was evaporated and the residue was distilled to yield 11.6 g (90%) of S-propargylthiobenzoate, bp 89-91°C/2 mm. $[d]_4^{20}$ 1.1461, n_D^{20} 1.5958. $C_{10}H_8OS$.

N-(4-Benzoylmercaptobut-2-inyl)piperidine (VII) was obtained from 0.02 mole of propargylthiobenzoate in the same way as compound V, yield 75%, $[d]_4^{20}$ 1.1049, n_D^{20} 1.5810. $C_{16}H_{19}NOS$.

Iodomethylates III-VI (general method). A 0.01-mole portion of the bases of III-VII was added to 0.1 mole of CH_3I in 10 ml of absolute ether and kept at room temperature for 24 h. The resultant precipitate was separated and vacuum-dried to yield the corresponding iodomethylates. The iodomethylate constants are given in Table 1.

EXPERIMENTAL (PHARMACOLOGICAL)

Muscarinolytic activity was measured on rat small intestine axial muscle. Activity on concentration curves defined the concentration of the methylfurmethide muscarine agonist (MFM) that causes a 50% muscular contraction (EC_{50}). The dissociation constant (K_D) of the antagonists was calculated by the Caddum formula [3]:

$$K_D = \frac{[B]}{OK - 1},$$

where [B] is the concentration of the competitive antagonist, OK is the ratio of the MFM EC_{50} in the presence of the antagonist to the MFM EC_{50} in the control.

One can see from the results given in Table 2 that one-half of the investigated compounds are muscarine antagonists. Compounds VI and VII exhibited the greatest muscarinolytic activity (about 0.1 μM). Replacement of the trimethylammonium group in the agonist IP-59 by a piperidine group (compounds III and the iodomethylate III) did not elicit muscarinolytic

activity in those compounds at a concentration of $2 \cdot 10^{-5}$ M. However, the introduction of a more bulky hydrophobic radical, such as anabasine, into the compound IP-59, as can be seen, converted this agonist into an antagonist (iodomethylate VI). By comparing the data in Table 2 one can say that the greater the "load" of the cationic head the higher the muscarinolytic activity of the investigated carboxylic butine esters (compare compounds VI and V, as well as the iodomethylates III and IV). The lytic effect is also increased by a factor of 10^2 when the acetyl group in the iodomethylate of N-(4-acetylmercaptobut-2-inyl)piperidine V is replaced by a benzoyl group (iodomethylate VII), i.e., when the acid portion of the agonist IP-59 analogs is "loaded."

One should note that muscarinolytic activity of the investigated substances is increased if the ester oxygen atom is replaced by a sulfur atom. For example, the transition from N-(4-acetoxybut-2-inyl)anabasine (IV) to N-(4-acetylmethylmercaptobut-2-inyl)anabasine (VI) is accompanied by a reduction in K_D by a factor of 10^2.

Thus, the introduction of large hydrophobic radicals both into the acid portion and cation head of the muscarine agonist IP-59 resulted in the appearance of two new active muscarine antagonists, namely N-(4-acetylmercaptobut-2-inyl)anabasine and iodomethylate N-(4-benzoylmercaptobut-2-inyl)piperidine.

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ANTIINFLAMMATORY PROPERTIES OF CERTAIN β-AMINOKETONE DERIVATIVES OF α-AMINO ACIDS

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Earlier we studied the antiinflammatory properties of a number of β-aminoketone derivatives of α-amino acids [1-4, 8]. Some of them, when injected intraperitoneally, exhibited antiinflammatory activity; however, when administered internally, their activity was low.

The purpose of this work was to study the analgesic properties (nonnarcotic type) of such β-aminoketones, as well as their influence on the development of fibrous granulation tissue during proliferative inflammation.

EXPERIMENTAL

The experiments were conducted on noninbred white rats of both sexes, weighing 100-120 g. The test substances were administered internally in the form of a suspension in a 1% starch slurry. The analgesic properties of the compound (nonnarcotic type) and the development of inflammatory edema were studied simultaneously in the presence of inflammatory edema of the paw of a rat induced by subplantar injection of a 20% suspension of yeast or a 0.5% solution of carrageenan [5, 10, 11]. A phlogogenic stimulant was introduced 1 h after the administration of the test substances; after 1 and 3 h the value of the edema of the paw and the pain sensitivity of its tissues were determined.

The influence of the compounds on the development of proliferative inflammation was studied on a model of "Pellet granuloma" [9]. Inhibition of inflammatory edema, pain sensitivity, and the development of proliferative inflammation was determined in percent relative to the control. The fever-reducing properties of the compounds were studied on a model of yeast fever in rats [7].

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