4. Japanese Patent Application No. 61-205257, RZh. Khim. No. 20090P (1987).
5. L. S. Kaminskii, Statistical Processing of Laboratory and Clinical Data [in Russian], Leningrad (1964), pp. 17-35 .
6. Methodological Recommendations for the Experimental (Preclinical) Study of Nonsteroid Antiinflammatory Pharmacological Agents [in Russian], Moscow (1983).
7. US Patent No. 4,623,662; RZh. Khim., No. 14050P (1987).
8. I. Litchfield and F. Wilcoxon, J. Pharm. Exp. Ther., 96, 99-113 (1949).
9. L. O. Randal and J. Selitto, Arch. Int. Pharmacodyn., 111, 409-419 (1957).
10. C. A. Winter, E. A. Risley, and G. W. Nuss, Proc. Soc. Exp. Biol. (NY), 111, 544-547 (1962).

SYNTHESIS AND ANESTHETIC ACTIVITY OF ACETOMESIDIDES CONTAINING TROPANE AND PIPERIDINE FRAGMENTS

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Among the aminoacetyl derivatives of 2,6-dimethyl- and 2,4,6-trimethylanilines a large group of highly active anesthetics is known, which are in use at the present time (lidocaine, trimecaine, marcaine, etc.).

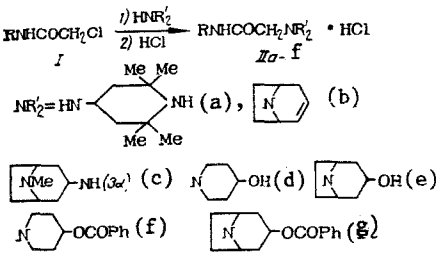
The search for anesthetics in this direction is of great interest, as indicated by new investigations in this series of compounds [2] directed to the use of cyclic amines as the amine components in the structure of these compounds.

In order to carry out the search for anesthetic compounds, we synthesized acetomesidides with fragments of substituted piperidines and tropanes (IIa-g).

The aminoacetyl derivatives of 2,4,6-trimethylaniline IIa-e were obtained by amination of chloroacetomesidide (I) with corresponding amines. The amination of chloroacetomesidide with 2,2,6,6-tetramethyl-4-piperidylamine proceeds only at the primary amino group, since the secondary amino group is in a screened position [4].

Compounds IIf, g containing two anesthesiophore groupings (the aminoacetomesidide and ester groups) in combination with piperidine and tropane rings were obtained by benzoylation of compounds IId, e.

At a 1:2 molar ratio of IId and benzoyl chloride, up to 30% of a dibenzoyl derivative is formed, which was identified mass-spectroscopically (M^+ = 484).



R = 2,4,6-trimethylphenyl

EXPERIMENTAL (CHEMISTRY)

The mass spectra were run on a "Varian MAT-112" spectrometer at 70 eV. The temperature of the ionization chamber was 250°C. The purity of the compounds was determined on a Tsvet-152 chromatograph (column 0.7 m long, 6 mm in diameter, N-AW chromatone solid carrier, 0.25

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TABLE 1. Characteristics of Hydrochlorides of Amino Derivatives of Acetomesidides IIa-g

Compound	Yield, %	Mp, °C	Empirical formula	M^+
IIa	91	231—3	$C_{20}H_{33}N_3O \cdot HCl$	330
IIb	44	102—4	$C_{18}H_{24}N_2O \cdot HCl$	283
IIc	66	190—2	$C_{19}H_{29}N_3O \cdot 2HCl$	314
IId	62	106—8	$C_{16}H_{25}N_2O_2 \cdot HCl$	276
IIe	78	129—32	$C_{18}H_{26}N_2O_2 \cdot HCl$	301
IIf	84	110—12	$C_{23}H_{29}N_2O_3 \cdot HCl$	379
IIg	88	216—18	$C_{25}H_{30}N_2O_3 \cdot HCl$	406

TABLE 2. Comparative Activity during Surface Anesthesia of Compounds IIb,e,g, Dicaine and Pyromecaine

Compound	Anesthesia		
	time of setting in, min	depth (the Regnier index)	duration of action, min
IIb	1±0,2	1300,0±0,0	55,0±2,5
IIc	3,5±1,5	736,9±8,23	32,0±1,6
IIg	1,0±0,4	1048,6±12,9	46,0±5,6
Dicain	1,0±0,2	1300±0,0	60,0±0,0
Pyromecaine	1,0±0,5	1300,0±0,0	54,5±5,2

Note. Experiments were carried out on the cornea of a rabbit by the Regnier method. Mean data of 8 experiments with a standard error, averaged for 1% solutions are given.

TABLE 3. Comparative Activity of Compounds IIb,e,g, Novocaine, and Trimecaine during Conduction and Infiltration Anesthesia

Compound	Depth of anesthesia (in %) after				K (experiment/background) after 30 min
	5 min	15 min	30 min	60 min	
Conduction anesthesia					
IIb	100,0	100,0	45,0	29,0	1,8
IIc	100,0	100,0	100,0	47,5	4,0
IIg	46,0	100,0	100,0	46,0	4,0
Novocaine	28,0	30,0	32,0	24,0	1,3
Trimecaine	100,0	100,0	100,0	30,0	4,0
Infiltration anesthesia					
IIb	100,0	100,0	49,8	27,0	2,0
IIc	100,0	100,0	100,0	40,8	4,0
IIg	61,0	100,0	100,0	30,8	4,0
Novocaine	35,0	34,5	32,0	29,0	1,3
Trimecaine	72,5	100,0	87,2	40,0	3,5

Note. Mean data of 6 experiments for 2% solutions are given; a fourfold increase in the threshold was accepted as 100%.

mm, liquid phase SE 30/5 %). Conditions: evaporator temperature 300°C, temperature programming of the thermostat 75-250°C (10°C in 1 min), flow rate of nitrogen 60 ml in 1 min. The melting points were determined on a Boetius microheater. The characteristics of the synthesized compounds are given in Table 1. The values of the elemental analyses found correspond to the calculated ones.

Preparation of Aminoacetomesidides (IIa-e). A mixture of 0.045 mole of chloroacetomesidide [1], 0.045 mole of the corresponding amine, and 0.045 mole of Et_3N was boiled for 4 h in 60 ml of toluene. The hot solution was then filtered from $Et_3N \cdot HCl$ and evaporated, and the residue was recrystallized from toluene, washed with anhydrous ether, and dried. The product obtained was dissolved in alcohol and converted into the hydrochloride.

4-Benzoyloxypiperidinoacetomesidide (IIf). A solution of 1.26 g (0.009 mole) of benzoyl chloride in 15 ml of benzene was added dropwise at room temperature to a solution of 2.47 g (0.009 mole) of the piperidinoacetomesidide base (IId) in 15 ml of benzene. The mixture was then heated for 3 h at 60-70°C. After cooling, the solution was decanted, and the residue was ground with dry ether, thoroughly washed with ether, and dried. Yield, 3.15 g of IIf.

3-Benzoyloxynortropanoacetomesidide (IIg). A 4-g portion (0.012 mole) of a hydrochloride of nortropanomesidide (IIe) was heated with 2.1 g (0.015 mole) of benzoyl chloride in 4 ml of toluene at 110-115°C for 5 h. At the end of heating the precipitate was ground with ether, washed, and dried. Yield, 4.6 g of IIg.

EXPERIMENTAL (PHARMACOLOGY)

The general effect, acute toxicity, the anesthetic and local-irritating action of compounds IIa-g was studied.

The tests were carried out on white mice weighing 18-20 g each and rabbits weighing 2.2-2.5 kg each. The ability of the compounds to cause surface anesthesia was determined on rabbits using the Regnier method [6], conduction and infiltration anesthesia on mice (the modified Bianchi method) using the "tail flick" test [5], and the "pain-producing method" in rabbits [3].

In tests on mice, a noniceptive stimulation of the tail was applied using the "Analgesia test, tail-flick type 812, Hugo Sachs Electronic" apparatus. The compounds in a volume of 0.05 ml were administered subcutaneously to mice from the dorsal side of the tail, 1 cm below its root. The latent period of the tail flicking was recorded during a thermal stimulation directly at the site of the administration of the compound (for the evaluation of the level of the infiltration anesthesia) or a thermal stimulation below the site of the administration of the compound, at the tail end (to evaluate the level of conduction anesthesia). The local irritating effect was observed on the cornea of a rabbit according to Setnicar [7].

Cocaine, dicain, and pyromecaine were used as reference compounds during the surface anesthesia, and novocaine and trimecaine during the conduction and infiltration anesthesia.

The pharmacological evaluation showed that in all the above types of anesthesia, compounds IIb, e, g have the highest activity, while the remaining compounds are considerably inferior in their activity.

Compound IIb is most active in the surface anesthesia, and in its action it is not inferior to dicain and pyromecaine (Table 2).

Compounds IIe and IIg are somewhat less active in surface anesthesia.

In tests on mice during the conduction and infiltration anesthesia, a high activity was also exhibited by tropane derivatives IIb, e, g (Table 3). Compound IIe displayed the highest activity for these types of anesthesia, which was comparable with the action of trimecaine and surpassed the action of novocaine by more than three times. Compounds IIb, g approach trimecaine in their activity.

Similar results were obtained in tests on rabbits. With respect to the starting time, depth and duration of the anesthetic action, compounds IIb, e, g are close to trimecaine. The remaining compounds have a weakly pronounced activity during conduction and infiltration anesthesia.

In the determination of acute toxicity, it was found that the compounds studied are relatively slightly toxic (the LD_{50} during intraperitoneal administration to white mice is 140-190 mg/kg) and do not have a local-irritating action on conjunctival application to rabbits.

The results obtained lead us to the conclusion that acetomesidides containing a fragment of piperidine and tropane have anesthetic activity. Derivatives of tropane are more active than the corresponding derivatives of piperidine. Compound IIb showed the highest activity in surface anesthesia, and compound IIe in conduction and infiltration anesthesia.

LITERATURE CITED

1. S. V. Zhuravlev and V. D. Chugaeva, Med. Prom-st', No. 3, 21 (1958).

2. Spanish Patent No. 513,980 (1982); Chem. Abstr., 100, 34424 (1984).
3. N. T. Pryanishnikova and P. A. Sharov, Pyromecaine. Pharmacology and Clinical Application [in Russian], Moscow (1967), p. 21.
4. L. N. Yakhontov, Usp. Khim., No. 8, 1304 (1984).
5. C. Bianchi, Br. J. Pharmacol., 11, 104-106 (1956).
6. J. Regnier, C. R. Acad. Sci. (Paris), 177, 558-561 (1923).
7. J. Setnicar, Arzneim.-Forsch., 16, 623 (1966).

SYNTHESIS OF IMIDAZO[4,5-f]- AND [5,4-g]QUINOLINE DERIVATIVES

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We have previously [2] shown that substituted 5-nitrobenzimidazoles readily react with benzyl cyanide to form the corresponding condensed anthranils whose reduction results in 4-benzoyl-5-aminobenzimidazoles (Ia, b). The presence of a bicyclic aromatic amino group in position 5 makes it possible to use these compounds to synthesize derivatives of quinolone-4-carboxylic-3-acid that are condensed with the imidazole ring. The high level of antibacterial activity exhibited by substituted quinolone-4-carboxylic-3-acid is well recognized [1, 4]. A number of highly active drugs has been found in this series, and continuing efforts are being made to find chemotherapeutic agents among these types of compounds [2, 3].

The purpose of the present work was to synthesize derivatives of imidazo[5,4-g]quinoline that contain a 1-ethyl-3-carboxyquinolone-4 fragment and that represent analogs of the well-known drug, oxolinic acid [3].

In accordance with the usual synthesis of this type [3], we first condensed compounds Ia, b with ethoxymethylene malonate (II), which resulted in high yields of the corresponding enamines (IIIa, b). However, when we attempted to cyclize these compounds in polyphosphoric acid (one of the most frequently used condensing agents in the synthesis of quinolone carboxylic acids) [4] there was an unexpected reaction that results in the formation of imidazo-[4,5-f]quinoline derivatives (IVa, b) (see [3]). Apparently, this was due to a decarbethoxylation of one of the ethoxycarboxyl groups in the β-position of the enamine that resulted in cyclization upon the participation of the enamine β-carbon atom and a carbonyl of the benzoyl group. The structure of the synthesized tricyclic compounds was obtained from the mass-spectra data in which we observed peaks of molecular M^+ and fragmentary ions $[M - C_2H_4]^+$, $[M - C_2H_5]^+$, $[M - OC_2H_5]^+$, $[M - COOC_2H_4]^+$, $[M - COOC_2H_5]^+$, and the NMR-^{1}H spectra which are most characterized by the presence of two signal doublets in the 7.8-8.4 ppm region with a spin–spin reaction constant of ≈9 Hz relative to the ortho-protons of the benzene ring, and IR spectra which exhibited absorption of the aromatic complex ester groups at ≈1690 cm^{-1}. Element analysis data were also used to verify the compounds' structure.

Saponification of the complex ester groups in an alkaline medium results in the formation of the corresponding carboxylic acids (Va, b).

We found that the best method for another type of cyclization was to heat the enamines IIIa, b in a mixture of polyphosphoric acid (PPA) and phosphorus oxychloride in which case good yields were obtained of the targeted derivatives of imidazo[5,4-g]quinoline (VIa, b). One should note that imidazoxyquinolone VIb was also synthesized by heating enamine IIIb in diphenyl oxide. By ethylating imidazoquinolone VIa with ethyl iodide in DMF in the presence of KOH we succeeded in obtaining two products (VIIa, VIII) whose structures we established for the first time by NMR-^{1}H spectra (see Experimental for NMR-^{1}H spectral data). The NMR-^{1}H spectral data and element analysis data indicated that compounds VIIa, VIII are N- and O-ethyl derivatives of imidazoquinolone VIa.

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