The isomeric compositions of the products of nitration of 2-methylcoumaran and chroman with acetyl nitrate were determined. More convenient methods for the synthesis of 7-amino-2-methylcoumaran and 8-aminochroman were developed, and 9-amino-1-benzoxepane was obtained for the first time. Alkylaminoacylamino-substituted 2-methylcoumarans, chromans, and 1-benzoxepanes were synthesized. A method for the synthesis of 2-bromocaproyl chloride from caproic acid was developed.

Amino-substituted coumarans, chromans, and benzoxepanes are of interest for the synthesis of physiologically active substances [1-4]; however, convenient methods for obtaining many amines of this type are not available. Thus 7-amino-2-methylcoumaran (IIb) was obtained by catalytic hydrogenation of its benzofuran analog by heating under pressure [3, 4], and 8-aminochroman (IVb) was synthesized by a multistep method [5]. We have developed simpler methods for obtaining amines IIb and IVb, which consist in the nitration of 2-methylcoumaran and chroman with acetyl nitrate with subsequent reduction of the resulting mixtures of nitro derivatives Ia and IIa (in a ratio of 3:2) and, respectively, IIIa with IVa (in a ratio of 1:3) and chromatographic separation on silica gel of the resulting mixtures of amines Ib with IIb and IIIb with IVb into individual compounds. In the nitration with a mixture of nitric and acetic acids 2-methylcoumaran forms virtually only one nitro derivative (Ia), while chroman forms a mixture of isomers IIIa and IVa in a ratio of 4:1 [6]. The tendency of acetyl nitrate to nitrate an aromatic ring in the ortho position relative to a substituent that contains an unshared pair of electrons is well known [7]. Under the conditions that we used 1-benzoxepane is not nitratred by acetyl nitrate, but amino derivatives Vb and VIb were obtained by the pathway indicated above from the mixture of its nitro derivatives Va with VIA (in a ratio of 2:1) formed by nitration with 70% nitric acid [6].

The possibility of the formation by isomers IIb, IVb, and VIb of an intramolecular hydrogen bond with the participation of the oxygen atom of the heteroring, which decreases their ability to be adsorbed on silica gel [8], assists in the chromatographic separation of mixtures of amines Ib with IIb, IIIb with IVb, and Vb with VIb.

By acylation of amines Ib-Vb with 2-bromocaproyl chloride (VII), which was obtained by bromination of caproyl chloride, we synthesized N-(2-bromocaproyl)amino derivatives Ic-Vc and converted them to N-(2-alkylaminocaproyl)amino derivatives Id, IIId, and Ie-Ve by reaction with methyl- or diethylamine. Cyclic analogs If and IIIf were synthesized from amines Ib and, respectively, IIIB by the successive action of methylmagnesium iodide and ethyl N-n-butylpipecolinate (VIII), which was obtained by our modified method for the synthesis of the N-methyl analog [9].

Compounds Id-f, Ile, IIIId-f, IVe, and Ve display local-anesthetizing action and surpass known 6-alkylamino-acylaminochromans [2] in activity. The most active compound, viz., Ile hydrochloride, is less toxic and, under conditions of infiltration anesthesia, more active than novocaine.

EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The IR spectra of mineral oil suspensions were obtained with a UR-20 spectrometer. The PMR spectra of solutions in CCl₄ were recorded with a Tesla BS-387C spectrometer (80 MHz) with tetramethylsilane (TMS) as the internal standard. The ratios of the isomers were determined with an LKhM-8MD chromatograph: the column was 3-m long, the stationary phase was 9% silicone rubber on Chromosorb W-AW, the carrier gas was helium, and the column temperature was 200-250°C.

The starting 1-benzoxepane, 2-bromo-6-chlorocaproic acid, 2-methylcoumaran, and chroman were synthesized by the methods in [6, 9-11]. Compounds Ia [6], Ib [3, 4, 12], IIb [3, 4], IIIa, b [2, 5], IVa [6], IVb [5], Vb [3], and VII [14] were previously described.

The characteristics of the new compounds are presented in Tables 1 and 2.

Nitro Derivatives Ia-IVA. A mixture of 2.5 ml (60 mmole) of 100% HNO₃ and 30 ml of acetic anhydride was maintained at 20°C for 30 min, after which it was added dropwise at 10°C to a solution of 4.7 g (35 mmole) of 2-methylcoumaran or chroman in 15 ml of acetic anhydride, and the resulting mixture was stirred at 20°C for 30 min. It was then poured into water, and the aqueous mixture was extracted with chloroform. The extract was washed with Na₂CO₃ and water, dried over Na₂SO₄, and passed through a thin layer of silica gel. The solvent was removed by distillation to give ~5.6 g (90%) of a mixture of isomers la with IIIa or IVa (75-80% yields), which was dissolved in benzene-ether (1:1) and passed through a column of silica gel. The eluant was evaporated to give the compound in the form of an oil, which was recrystallized from hexane to give a pure crystal.

Nitro Derivative IIIa. This compound could not be isolated in individual form. The structure was assigned to it from the PMR spectrum of a mixture of the isomers and on the basis of its conversion to amine IIb by reduction.

Nitro Derivatives Va and VIa. A mixture of these compounds was obtained by the methods in [6].

Amino Derivatives Ib-VIIb. A 2.5-ml (25 mmole) sample of concentrated HCl was added in the course of 30 min to a refluxing solution of 30 mmole of a mixture of nitro compounds Ia with IIIa, IIIa with IVa, or Va with VIa in 80 ml of 80% ethanol containing 11.2 g (200 mmole) of iron powder and 1.3 g (20 mmole) of copper powder, after which the mixture was stirred and refluxed for another 3 h. It was then filtered, and the filtrate was cooled to 20°C and acidified with concentrated HCl. The ethanol was removed by distillation, and the residue was made alkaline with KOH solution and extracted with ether. The extract was dried over Na₂SO₄, and fractionated to give a mixture of amines Ib with IIb, IIIb with IVb, or Vb with VIb (75-80% yields), which was dissolved in benzene-ether (1:1) and passed through a column of silica gel.