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SYNTHESIS OF AMINO-SUBSTITUTED 2-METHYLCOUMARINS, CHROMANS, AND BENZOXEPANES AND THEIR N-(ALKYLAMINOACYL) DERIVATIVES

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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 nitrated 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.

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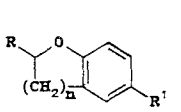
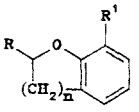


I, III, V



II, IV, VI

I, II n=1, R=CH_3; III, IV n=2, R=H; V, VI n=3, R=H; I–VI a R^1=NO_2; b R^1=NH_2;

c R^1=NHCOCHBr–C_4H_9; d R^1=NHCOCHNHCH$_3$ (C_4H_9); e R^1=NHCOCHHN(C_2H_5)$_2$ (C_4H_9); f R^1=NHCO– (N–C_4H_9)

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, IIe, IIId-f, IVe, and Ve display local-anesthetizing action and surpass known 6-alkylamino-acylaminochromans [2] in activity. The most active compound, viz., IIe 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 CCl_4 were recorded with a Tesla BS-487C 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], Va, b [13], VIa [6], 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% HNO_3 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 Na_2CO_3 and water, dried over Na_2SO_4, 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 Ia with IIa or IIIa with IVa, by recrystallization of which from hexane or ethanol isomer Ia or IIIa could be isolated.

Nitro Derivative IIa. 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-VIb. 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 IIa, 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 Na_2SO_4 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

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp,[a] °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, ν, cm^{-1}		Found, %				Empirical formula	Calc., %				Yield, %
			C=O	NH	C	H	Hal	N		C	H	Hal	N	
VIb	213—215	211 (4,30), 239 (3,80), 321 (3,21)	—	—	59,9	7,3	17,9	6,8	$C_{10}H_{13}NO \cdot HCl$	60,1	7,1	17,8	7,0	10[b]
Ic	75—76	207 (4,21), 278 (3,92)	1650	3275	55,3	6,4	24,6	4,3	$C_{15}H_{20}BrNO_2$	55,2	6,2	24,5	4,5	90
IIc	107—108	207 (4,29), 251 (3,84), 296 (3,80)	1660	3255	55,4	6,2	24,3	4,4	$C_{15}H_{20}BrNO_2$	55,2	6,2	24,5	4,5	90
IIIc	106—107	208 (4,22), 275 (3,99)	1660	3300	55,3	6,1	24,4	4,2	$C_{15}H_{20}BrNO_2$	55,2	6,2	24,5	4,5	80
IVc	64—65	210 (4,18), 257 (3,88), 296 (3,78)	1685	3380	55,2	6,0	24,3	4,4	$C_{15}H_{20}BrNO_2$	55,2	6,2	24,5	4,5	85
Vc	107—108	210 (4,32), 266 (4,08)	1655	3280	56,8	6,6	23,6	4,1	$C_{16}H_{22}BrNO_2$	56,5	6.5	23,5	4,1	80
Id	184—185	209 (4,28), 260 (4,10)	1665	3230	61,1	8,1	11,6	8,7	$C_{16}H_{24}N_2O_2 \cdot HCl$	61,4	8,0	11,3	9,0	90
IIId	183—184	208 (4,54), 256 (4,33)	1685	3270	61,4	8,3	11,1	9,2	$C_{16}H_{24}N_2O_2 \cdot HCl$	61,4	8,0	11,3	9,0	90
Ie	143—144	209 (4,45), 263 (4,25)	1660	3230	64,2	8,8	10,1	7,9	$C_{19}H_{29}N_2O_2 \cdot HCl$	64,3	8,8	10,0	7,9	72
IIe	135—136	217 (4,36), 249 (4,05), 293 (3,85)	1700	3180	64,6	8,8	10,1	7,9	$C_{19}H_{29}N_2O_2 \cdot HCl$	64.3	8,8	10,0	7,9	75
IIIe	163—164	208 (4,46), 261 (4,11)	1670	3200	64,3	8,6	10,0	7,7	$C_{19}H_{29}N_2O_2 \cdot HCl$	64,3	8,8	10,0	7,9	73
IVe	79—80	216 (4,30), 250 (4,01), 293 (3,68)	1670	3170	64,1	8,6	9,9	7,8	$C_{19}H_{29}N_2O_2 \cdot HCl$	64,3	8,8	10,0	7,9	75
Ve	175—176	211 (4,32), 253 (4,17)	1680	3220	65,3	8,7	9,8	7,4	$C_{20}H_{31}N_2O_2 \cdot HCl$	65,1	9,0	9,6	7,6	75
If	217—218	210 (4,24), 263 (4,10)	1670	3200	64,4	8,3	10,2	7,6	$C_{19}H_{28}N_2O_2 \cdot HCl$	64,7	8,3	10,1	7,9	85
IIIf	183—184	210 (4,28), 262 (4,15)	1670	3210	65,0	8,2	10,4	7,9	$C_{19}H_{28}N_2O_2 \cdot HCl$	64,7	8,3	10,1	7,9	85
VIII	—[c]		1730	—	67,4	10,9	—	6,4	$C_{12}H_{23}NO_2$	67.6	10,9	—	6,6	51

[a]Crystallization solvents: ethanol for VIb, hexane for Ic-Vc, tetrafuran for Id and IIId, acetone for Ie, V
If, and IIIf, cyclohexane for IIe, 1-butanol for IIIe, and tetrachloromethane for IVe.
[b]Based on 1-benzoxepane.
[c]This compound had bp 77-78°C (1 mm) and n_D^{20} 1.4554.

TABLE 2. PMR Spectra of the Synthesized Compounds (δ, ppm)

Compound	CH_3[a]	CH_2	$(CH_2)_2$ or $(CH_2)_3$ (m)	CHAr or CH_2Ar	CH_2N or CH_3N	CHNa (t)	CHBra (t)	CHO or CH_2O	4-H	5-H	6-H	7-H	8-H (9-H)	NH or NH_2
IIa	d 1,42	—	—	dd 2,80[b] dd 3,37[b]	—	—	—	m 4,85—5,17	dd 7,45[c]	t 7,30[d]	dd 7,67[c]	—	—	—
VIb[e]	—	—	1,42—1,95	t 2,61[a]	—	—	—	t 3,77[a]	—	—	m 6,27—6,77 (ArH)			s 3,70
Ic	t 0,89 d 1,36	m 1,75—2,21	1,15—1,52	dd 2,60[b] dd 3,12[b]	—	—	4,35	m 4,57—4,90	dd 7,30[f]	—	dd 6,92[c]	d 6,47[d]	—	s 8,54
IIc	t 0,88 d 1,42	m 1,80—2,17	1,10—1,55	dd 2,71[b] dd 3,22[b]	—	—	4,25	m 4,62—5,02	m 6,52—6,75		dd 7,87[c]	—	—	s 8,85
IIIc	t 0,91	m 1,82—2,11	1,19—1,49	t 2,65[a]	—	—	4,35	t 4,05[a]	—	d 7,21[f]	—	dd 6,99[c]	d 6,55[d]	s 8,37
IVc	t 0,94	m 1,82—2,20	1,17—1,55	t 2,71[a]	—	—	4,31	t 4,20[a]	—	dd 6,77[c]	t 6,61[a]	dd 8,06[c]	—	s 8,49
Vc	t 0,87	m 1,52—2,12	1,17—1,50 1,52—2,12	t 2,64[a]		—	4,31	t 3,80[a]	—	—	d 7,19[f]	—	dd 7,09[c] (d 6,71[d])	s 8,44
Id[e]	t 0,85 d 1,27	—	1,10—1,72	dd 2,72[b] dd 3,24[b]	s 2,29	2,91	—	m 4,50—4,90	s 7,37	—	dd 7,05[c]	d 6,46[d]	—	m 2,50 2,75 s 9,16
IIId[e]	t 0,90	q 1,89[a]	1,15—1,45	t 2,66[a]	s 2,37	2,88	—	t 4,02[a]	—	d 7,25[f]	—	dd 7,04[c]	d 6,54[d]	s 1,55 s 8,92
Ie[e]	t 0,99 d 1,35	—	1,17—1,72	dd 2,60[b] dd 3,15[b]	q 2,54[a]	3,10	—	m 4,50—4,90	s 7,39	—	dd 6,98[c]	d 6,46[d]	—	s 9,06
IIe[e]	t 0,99 t 1,06 d 1,40	—	1,25—1,69	dd 2,72[b] dd 3,24[b]	q 2,52[a]	3,11	—	m 4,70—5,05	m 6,57—6,77		m 7,90—8,15	—	—	s 9,24
IIIe[e]	t 1,05	q 1,91[a]	1,15—1,60	t 2,56[a]	t 2,56[a]	3,12	—	t 4,04[a]	—	s 7,22	—	dd 6,99[c]	d 6,56[d]	s 8,90
IVe[e]	t 0,99 t 1,06	t 1,96[a]	1,25—1,69	t 2,71[a]	q 2,57[a]	3,16	—	t 4,17[a]	—	dd 6,52[c]	t 6,70[d]	dd 8,11[c]	—	s 9,51
Ve[e]	t 1,00	m 1,18—1,95	—	t 2,57[a]	q 2,52[a]	3,10	—	t 3,80[a]	—	—	m 7,10—7,30	—	m 7,10—7,30 (d 6,70[d])	s 8,97
If[e]	t 0,90 d 1,38	m 1,20—2,07		m 2,85—3,42	m 2,85—3,42	—	—	m 4,61—4,95	d 7,46 f	—	dd 7,25[c]	d 6,60[d]	—	s 8,22
IIIf[e]	t 0,91	m 1,17—2,17		m 2,42—2,92	m 2,42—2,92	—	—	t 4,10[a]	—	d 7,34 f	—	dd 6,96[c]	d 6,61[c]	s 8,19
VIII	t 0,90 t 1,21	m 1,24—1,90	—	—	m 2,06—2,61 m 2,81—3,25	—	—	q 4,05[a]	—	—	—	—	—	—

[a]Constant J = 5–6 Hz.
[b]Constants J = 8 and 16 Hz.
[c]Constants J = 3 and 9 Hz.
[d]Constant J = 9 Hz.
[e]Free base.
[f]Constant J = 3 Hz.

a column packed with L 100/160 silica gel (chemapol, Czechoslovakia). The first compound isolated was amine IIb, IVb, or VIb, followed by Ib, IIIb, or Vb (R_f 0.8 and, respectively, 0.3-0.4 on a plate coated with a 0.25-mm layer of the same brand of silica gel). The yields of amines Ib-V were, respectively, 37%, 25%, 16%, 47%, and 26%, based on the starting benzoxaheterocycles.

N-(2-Bromocaproyl)amino Derivatives Ic-Vc. A solution of one of the amines Ib-Vb and acid chloride VII (50 mmole of each) in 75 ml of anhydrous benzene was refluxed for 12 h, after which it was cooled, washed with 5% HCl and water, dried over Na_2SO_4, and distilled to remove the benzene.

N-(2-Alkylaminocaproyl)amino Derivatives Id, IIId, and Ie-Ve. A solution of 10 mmole of one of the derivatives Ic-Vc in 50 ml of benzene containing 6.2 g (200 mmole) of methylamine or 3.7 g (50 mmole) of diethylamine was maintained at 20°C for 150 h or, respectively, refluxed for 30 h, after which it was extracted with 5% HCl. The extract was made alkaline with K_2CO_3 and extracted with benzene. The extract was dried over Na_2SO_4 and concentrated. The residue was dissolved in absolute ether, and the hydrochlorides of Id, IIId, and Ie-Ve were precipitated by bubbling in anhydrous hydrogen chloride.

N-(N-n-Butylpipecolinyl)amino Derivatives If and IIIf. These compounds were synthesized by a procedure similar to that used to obtain 1,3,5-trimethyl-2-(N-methylpipecolinyl)-aminobenzene [9].

2-Bromocaproyl Chloride (VII). A mixture of 116 g (1 mole) of caproic acid and 154 g (1.3 mole) of thionyl chloride was heated at 100°C for 3 h, after which heating was discontinued, a small crystal of iodine was added, and 192 g (1.2 mole) of bromine was added at such a rate that the liberated hydrogen bromide did not carry away bromine vapors through the condenser. The mixture was then heated at 100°C for 2 h, after which it was fractionated to give 160 g (75%) of VII with bp 84-86°C (20 mm).

Ethyl-N-n-Butylpipecolinate (VIII). A solution of 36.6 g (500 mmole) of n-butylamine and 11.5 g (50 mmole) of 2-bromo-6-chlorocaproic acid in 200 ml of anhydrous benzene was maintained at 20°C for 25 h, after which it was concentrated, and the residue was dissolved in 60 ml of absolute ethanol. The ethanol solution was saturated with anhydrous hydrogen chloride, maintained at 20°C for 250 h, and concentrated. The concentrate was maintained for 5 h in vacuo (10-15 mm) at 80°C, after which it was dissolved in 50 ml of absolute ethanol. The solution was treated with 4.7 g (40 mmole) of thionyl chloride, after which the mixture was maintained at 20°C for 50 h and then concentrated. The residue was neutralized with 40% K_2CO_3 solution, the mixture was extracted with dichloromethane, and the extract was washed with water, dried over Na_2SO_4, and distilled.

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