SYNTHESIS OF METHYL-SUBSTITUTED 4-AMINOMETHYL-4-BUTANOLIDES AND 5-HYDROXY-2-PIPERIDONES

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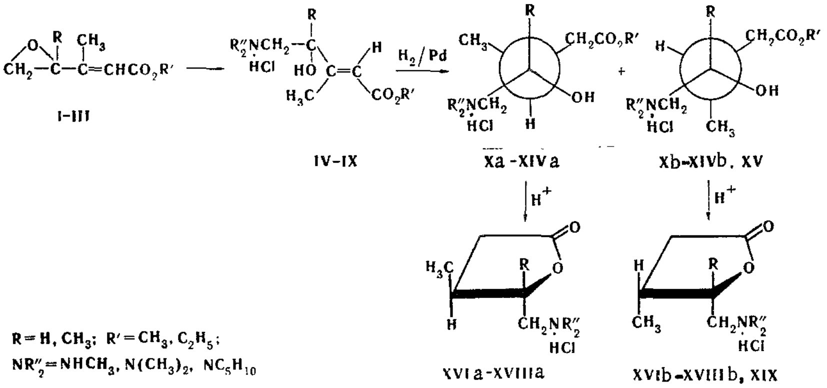
UDC 547.722.3'724'824:541.63:
543.422.25.4

Esters of 5-amino-4-hydroxy-3-methylvaleric acids, which exist as pairs of diastereomers and are readily converted to the corresponding methyl-substituted 4-aminomethyl-4-butanolides or 5-hydroxy-2-piperidones, are obtained by reaction of esters of 3-methyl-4, 5-epoxy-2-pentenoic acid with amines and subsequent hydrogenation of the resulting esters of 5-amino-4-hydroxy-3-methyl-2-pentenoic acids.

In a continuation of our study of the reactivities of the methyl-substituted 4, 5-epoxy-2-alkenoic acid esters that we synthesized in [1] we accomplished the conversion of 3-methyl-4, 5-epoxy-2-pentenoic acid esters (I-III) to 4-aminomethyl-4-butanolides XVIa,b-XVIIIa,b and XIX, which have physiological activity [2]:



5-Dialkylamino-4-hydroxy-3-methyl-2-pentenoic acid esters (IV-IX) are formed in the reaction of epoxides I-III with amines. The absorption band of a hydroxyl group at 3400-3430 cm^{-1} in the IR spectra of the latter does not change its position when the solution is diluted to 10^{-3} M, and this indicates an intramolecular hydrogen bond with the nitrogen atom [3]. The PMR spectra of esters IV-IX are in agreement with the structure of the latter and show that the E isomer is formed as a result of the reaction [1].

Hydrogenation of hydrochlorides IV-IX over palladium hydroxide on carbon proceeds with the absorption of an equimolar amount of hydrogen and gives a mixture of hydrochlorides of the diastereomeric 5-amino-4-hydroxy-3-methylvaleric acid esters (Xa, b-XIVa, b and XV). The ratio of the individual hydrochlorides of both diastereomeric forms isolated by fractional crystallization (we were able to isolate only one isomer in the case of XV) depends on the nature of the ester and the dialkylamino group. The transition from the methyl ester to the ethyl ester with retention of the same dialkylamino group is associated with an increase in the relative percentage in each pair of diastereomer a, which has a high melting point. Absorption bands of an ester carbonyl group at 1735-1745 cm^{-1} and of a hydroxyl group at 3300-3500 cm^{-1} are observed in the IR spectra of hydrochlorides Xa, b-XIVa, b and XV, and the absorption band of a double bond is absent. The action of alkaline agents on these hydrochlorides gives mixtures of δ-amino-γ-hydroxy acid esters with their corresponding lactones and lactams, but 4-aminomethyl-3-methyl-4-butanolide

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V. I. Lenin Belorussian State University, Minsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 594-598, May, 1975. Original article submitted November 28, 1973; revision submitted June 18, 1974.

TABLE 1. Chemical Shifts of the 3- and 4-CH_3 Protons in the PMR Spectra of 4-Butanolides XVIa, b, XVIIa, b, and XIX

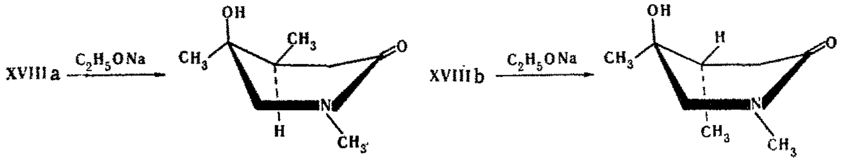
Compound	Chem. shift, δ, ppm	
	3-CH_3*	4-CH_3
XVIa	1,05	1,24
XVIb	0,98	1,11
XVIIa	1,06	1,21
XVIIb	0,98	1,11
XIX	0,97	4,04†

* Doublet, J = 7 Hz.

†Quartet (4-H), $J_{3,4}$ = 6 Hz.

hydrochlorides (XVIa, b-XVIIIa, b and XIX) are formed when acidified (with hydrochloric acid) aqueous or methanol solutions of the above-indicated hydrochlorides are refluxed. The absorption band of a carbonyl group is observed at 1785-1795 cm^{-1} in the IR spectra of lactones XVIa, b, XVIIa, b, and XIX, isolated by the action of alkalis on their hydrochlorides, and of lactone hydrochlorides XVIIIa, b (this is characteristic for saturated γ-lactones), and the band of hydroxyl absorption is absent. The signals of the 3- and 4-CH_3 groups are found at weaker field in the PMR spectra of lactones XVIa and XVIIa, which have higher melting points than the corresponding isomeric XVIb and XVIIb, than in the spectra of XVIb and XVIIb (see Table 1); this is an indication of trans orientation of the 3-H and 4-CH_3 groups in XVIa and XVIIa and cis orientation in XVIb and XVIIb [4]. The consequent cis orientation of the 3- and 4-CH_3 groups in XVIa and XVIIa is confirmed by coincidence of their chemical shifts with the literature data from the PMR spectra of structurally similar lactones [5]. Lactone XIX has a cis structure, which follows from a comparison of its PMR spectrum with the spectra of XVIa, b and XVIIa, b and similarly constructed lactones [4] and is also in agreement with the $J_{3,4}$ constant (6 Hz) characteristic for cis orientation of 3-H and 4-H in 4-butanolides [6].

Stereoisomeric 5-hydroxy-1,4,5-trimethyl-2-piperidones (XXa, b) are formed when hydrochlorides XVIIIa, b are treated with an equivalent amount of alkali:



XXa XXb

Absorption bands of a δ-lactam carbonyl group at 1640-1660 cm^{-1} and of bonded (3400 cm^{-1}) and free (3620 cm^{-1}) hydroxyl groups are observed in the IR spectra of piperidones XXa, b. The signal of the 4-H proton in the PMR spectrum of XXa is a multiplet with a width of 23 Hz, which attests to its axial orientation [7]. The width of the multiplet of the same proton (17 Hz) in the PMR spectrum of isomeric XXb indicates equatorial orientation of the latter. The shift of the signal of the 4-H proton in piperidone XXb to weaker field as compared with the same signal in the spectrum of XXa is associated with equatorial orientation of the 4-H proton in XXb. The vicinal $J_{3,4}$ constants (7 and 11 Hz in the spectrum of XXa, and 4 and 8 Hz in the spectrum of XXb) were established by means of nuclear magnetic double resonance (NMDR); the values obtained are in agreement with a compressed boat conformation for piperidones XXa and XXb. The geminal constant of the protons of the 3-CH_2 group in XXb is 18 Hz; this may be explained by the contribution of the π system of the carbonyl group of the lactam ring to the distorted boat conformation [8]. Thus piperidone XXa has equatorially oriented 4- and 5-CH_3 groups, whereas XXb has an equatorially oriented 5-CH_3 group and an equatorially oriented 4-H proton; this is in agreement with the above-indicated configuration of the corresponding lactone hydrochlorides (XVIIIa, b).

EXPERIMENTAL METHOD

The IR spectra of thin films, CCl_4 solutions, or KBr pellets of the compounds were measured with a UR-20 spectrometer. The PMR spectra of 10% CCl_4 or $CHCl_3$ solutions were obtained with a Varian HA-100-15D spectrometer with tetramethylsilane as the internal standard. The NMDR spectra of 10% solutions of XXa and XXb in $CHCl_3$ were obtained with a JNM-100 PS spectrometer.

Methyl (I) and Ethyl (II) 3,4-Dimethyl-4, 5-epoxy-2-pentenoate and Methyl 3-Methyl-4, 5-epoxy-2-pentenoate (III). These esters were obtained by the method in [1] and had the following physical constants: I bp 80-82°(15 mm), d_4^{20} 1.0652, and n_D^{20} 1.4608; II bp 88-90° (12 mm), d_4^{20} 1.0291, and n_D^{20} 1.4544; III bp 45-49° (2 mm), d_4^{20} 1.0887 and n_D^{20} 1.4755.

5-Amino-4-hydroxy-3-methyl-2-pentenoic Acid Esters (IV-IX, Table 2). A solution of 0.2 mole of ester I-III and 0.2 mole of amine in 100 ml of methanol or ethanol (depending on the type of ester) was maintained at 18-20° for 5-7 days. The solvent was removed by distillation, the residue was dissolved in 400 ml of absolute ether, and dry hydrogen chloride was bubbled through the solution until it was slightly

TABLE 2. 5-Amino-4-hydroxy-3-methyl-2-pentenoic Acid Esters (IV-IX) and 4-Aminomethyl-3-methyl-4-butanolides (XVIa, b, XVIIa, b, and XIX)

Compound	R	R′	NR″$_2$	mp or bp, °C (mm)	d^{20}_4	n^{20}_D	MR_D		Empirical formula	N, %		Yield, %	Hydrochlorides, mp, °C
							found	calc.		found	calc.		
IV	CH_3	CH_3	$N(CH_3)_2$	80—81 (3)	1,0166	1,4735	55.31	55.22	$C_{10}H_{19}NO_3$	6.9	7,0	63	181
V	CH_3	C_2H_5	$N(CH_3)_2$	82—83 (2)	0,9962	1,4702	59.75	59,84	$C_{11}H_{21}NO_3$	6,3	6,5	46	164
VI	CH_3	CH_3	NC_5H_{10}	105—106 (2)	1.0322	1,4900	67.05	66.87	$C_{13}H_{23}NO_3$	5,8	5,8	58	179—180
VII	CH_3	C_2H_5	NC_5H_{10}	123—125 (3)	1,0181	1,4857	71,30	71.49	$C_{14}H_{25}NO_3$	5,6	5.5	48	197
VIII	CH_3	CH_3	$NHCH_3$	120 (6)	1.0561	1.4840	51.20	50,60	$C_9H_{17}NO_3$	7.3	7,5	32	167—168
IX	H	CH_3	NC_5H_{10}	42—43					$C_{12}H_{21}NO_3$	6,6	6.2	33	144—145
XVIa	CH_3		$N(CH_3)_2$	43					$C_9H_{17}NO_2$	8,1	8,2	80*	194
XVIb	CH_3		$N(CH_3)_2$	61 (2)	0,9926	1,4553	46,77	47.16	$C_9H_{17}NO_2$	8,3	8,2	59*	181—182
XVIIa	CH_3		NC_5H_{10}	41—42					$C_{12}H_{21}NO_2$	6,8	6.6	78*	202—203
XVIIb	CH_3		NC_5H_{10}	34—35					$C_{12}H_{21}NO_2$	6.5	6,6	70*	215
XIX	H		NC_5H_{10}	38					$C_{11}H_{19}NO_2$	7,5	7,1	58	229

* The yield given is based on the methyl ester of the corresponding 5-amino-4-hydroxy-3-methylvaleric acid.

TABLE 3. 5-Amino-4-hydroxy-3-methylvaleric Acid Ester Hydrochlorides (Xa, b-XIVa, b, XV) and 4-Methylamino-3,4-dimethyl-4-butanolide Hydrochlorides (XVIIIa, b)

Compound	R	R′	NR″$_2$	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
						N	Cl	N	Cl	
Xa	CH_3	CH_3	$N(CH_3)_2$	158—159	$C_{10}H_{21}NO_3 \cdot HCl$	5,9	15,1	5,8	14,8	42
Xb	CH_3	CH_3	$N(CH_3)_2$	103	$C_{10}H_{21}NO_3 \cdot HCl$	5.8	14,7	5,8	14,8	30
XIa	CH_3	C_2H_5	$N(CH_3)_2$	155	$C_{11}H_{23}NO_3 \cdot HCl$	5,7	14,1	5,5	14,0	44
XIb	CH_3	C_2H_5	$N(CH_3)_2$	108	$C_{11}H_{23}NO_3 \cdot HCl$	5,4	14,5	5,5	14,0	15
XIIa	CH_3	CH_3	NC_5H_{10}	155—156	$C_{13}H_{25}NO_3 \cdot HCl$	5,1	12,9	5,0	12,7	32
XIIb	CH_3	CH_3	NC_5H_{10}	140—141	$C_{13}H_{25}NO_3 \cdot HCl$	4,7	13,0	5.0	12,7	35
XIIIa	CH_3	C_2H_5	NC_5H_{10}	147	$C_{14}H_{27}NO_3 \cdot HCl$	4,6	12.3	4,8	12,1	36
XIIIb	CH_3	C_2H_5	NC_5H_{10}	132	$C_{14}H_{27}NO_3 \cdot HCl$	4,8	12,2	4.8	12,1	31
XIVa	CH_3	CH_3	$NHCH_3$	146	$C_9H_{19}NO_3 \cdot HCl$	5,9	15,7	6,2	15,7	30
XIVb	CH_3	CH_3	$NHCH_3$	123—124	$C_9H_{19}NO_3 \cdot HCl$	6,0	15,8	6.2	15,7	51
XV	H	CH_3	NC_5H_{10}	114—115	$C_{12}H_{23}NO_3 \cdot HCl$	5,7	13,3	5,3	13,4	50
XVIIIa	CH_3		$NHCH_3$	230	$C_8H_{15}NO_2 \cdot HCl$	7,4	18.6	7,2	18,4	93
XVIII	CH_3		$NHCH_3$	223—224	$C_8H_{15}NO_2 \cdot HCl$	7,1	18,6	7,2	18,4	98

acidic. The precipitated hydrochloride was separated and crystallized from acetone–methanol (or ethanol). Bases IV-IX were isolated by treatment of aqueous solutions of their hydrochlorides with a small excess of sodium hydroxide and extraction with ether. The ether extracts were dried with anhydrous magnesium sulfide, the ether was removed by distillation, and the residue was fractionated at reduced pressure. Ester VIII was crystallized from pentane.

PMR spectrum of ester V*: δ 1.13 (s, 4-CH_3), 2.21 [s, $N(CH_3)_2$], 1.21 (t, J = 7 Hz, ethyl CH_3) 2.40 and 2.57 (d, J = 13 Hz, CH_2N), 2.02 (d, J = 1.5 Hz, 3-CH_3), 3.63 (s, OH), 4.02 (q, J = 7 Hz, ethyl CH_2), and 6.08 ppm (q, J = 1.5 Hz, 2-H).

5-Amino-4-hydroxy-3-methylvaleric Acid Ester Hydrochlorides (Xa, b-XIVa, b and XV, Table 3). A solution of 0.1 mole of hydrochloride IV-IX in 80-100 ml of methanol was stirred vigorously in a hydrogen atmosphere in the presence of 1.5 g of a palladium catalyst on carbon [9] until 0.1 mole of hydrogen had been absorbed (2-3 h). The catalyst was removed by filtration, the methanol was removed by distillation, and the residue was separated into individual hydrochlorides Xa-XIVa, Xb-XIVb, and XV by fractional crystallization from acetone–methanol (5 : 1).

4-Aminomethyl-3-methyl-4-butanolides (XVIa, b-XVIIa, b and XIX, Table 2). A solution of 0.03 mole of hydrochloride Xa, b-XIIIa, b or XV in 5-10 ml of water was acidified to pH 1-2 with hydrochloric acid,

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* The following abbreviations are used here and subsequently: s is singlet, d is doublet, t is triplet, q is quartet, and m is multiplet.

and the mixture was refluxed for 1-2 h. Lactones XVIa, b, XVIIa, b, and XIX were isolated by treatment of the resulting solutions with a small excess of sodium hydroxide and extraction with ether. The ether extracts were dried with anhydrous magnesium sulfate, the ether was removed by distillation, and the residue was crystallized from pentane. Lactone XVIb was distilled at reduced pressure.

4-Methylaminomethyl-3, 4-dimethyl-4-butanolide Hydrochlorides (XVIIIa, b, Table 3). These compounds were obtained by refluxing acidified (with hydrochloric acid to pH 1-2) methanol solutions of hydrochlorides XIVa, b, subsequent removal of the methanol, and crystallization of the residue from methyl ethyl ketone–isopropyl alcohol.

5-Hydroxy-1,4,5-trimethyl-2-piperidones (XXa, b). A solution of 0.05 g-atom of sodium in 15 ml of absolute ethanol was added to a solution of 0.05 mole of hydrochlorides XIXa, b in 50-70 ml of absolute ethanol, the precipitated NaCl was removed by filtration, and the filtrate was vacuum evaporated. Piperidone XXa was crystallized from ethanol–ether to give a product with mp 91° in 62% yield. PMR spectrum: δ 0.96 (d, J = 7 Hz, 4-CH_3), 1.25 (s, 5-CH_3), 1.73-1.96 (m, 4-H), 2.24-2.35 (m, 3-CH_2), 2.88 (s, 1-CH_3), 3.16 and 3.30 (d, J = 14 Hz, 6-CH_2), and 4.01 ppm (s, OH). Found: N 8.8%. $C_8H_{15}NO_2$. Calculated: N 8.9%. Piperidone XXb was isolated by repeated extraction of the oily residue with warm ether and subsequent cooling of the extracts. The yield of product with mp 79-81° was 81%. PMR spectrum: δ 0.98 (d, J = 7 Hz, 4-CH_3), 1.25 (s, 5-CH_3), 2.02-2.14 (m, 4-H), 1.88-2.01 (m, 3-H), 2.77 (q, J_{vic} = 8 Hz, J_{gem} = 18 Hz, 3-H), 2.91 (s, 1-CH_3), 3.23 (s, 6-CH_2), and 3.86 ppm (s, OH). Found: N 8.9%. $C_8H_{15}NO_2$. Calculated: N 8.9%.

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