SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF CATIONIC AMINOACETYLENE FATTY ACID ESTER SURFACTANTS

M. S. Ergashev, A. G. Makhsumov, and P. Il'khamdzhanov

UDC 615.281:[547.582.2:547.295].012.1

In our previous reports we described the synthesis and properties of acetylene esters of fatty acids [3, 4].

As a continuation of those studies we synthesized aminoacetylene esters of fatty acids (IIIa-h) as well as their iodomethylates and hydrochlorides (IVa-h) according to the following pattern:

$$\underset{\text{Ia-h}}{RCOOCH_2C{\equiv}CH}+CH_2O+\underset{\text{II}}{HNMe_2}\longrightarrow\underset{\text{IIIa-h}}{RCOOCH_2C{\equiv}CCH_2NMe_2}$$

$$\xrightarrow[\text{or HCl}]{\text{MeI}}\underset{\text{IVa-h}}{RCOOCH_2C{\equiv}CCH_2NMe_2\cdot X},$$

where Ia: R = Me; Ib: R = Am; Ic: $R=C_7H_{15}$; Id: $R=C_9H_{19}$; Ie: $R=C_{11}H_{23}$; If: $R=C_{13}H_{27}$; Ig: $R=C_{15}H_{31}$; Ih: $R=C_{17}H_{35}$; IVa, b, e, g: X = MeI; IVc, d, f, h: X = HCl.

Compounds IIIa-h were synthesized by the aminomethylation of propargylic esters acetic, caproic, caprylic, capric, lauric, myristic, palmitic, and stearic acids (Ia-h) with the aid of $HNMe_2$ (II) and paraformaldehyde in an organic solvent in the presence of a copper acetate catalyst at a reaction medium temperature of 100-150°C for a period of 7 to 9 h. The products were purified by vacuum distillation as well as column chromatography.

Esters IIIa-h are liquid and crystalline substances with a low mp that are soluble in many organic solvents (Table 1).

The structures of all the synthesized compounds was established by element analysis as well as IR- and PMR-spectra data.

We examined the effect of various factors (temperature, catalyst, and solvent) on the final product yields in order to carry out the aminomethylation under optimal conditions.

The reaction medium temperature was significant. We found that the maximum yield of the aminoesters was reached when the temperature was increased to 100-110°C.

Our examination of the catalytic action of various copper salts in the aminomethylation reaction demonstrated that copper acetate and copper chloride were the most suitable catalysts. Aminomethylation in the presence of those catalysts resulted in a high aminoester yield, i.e., up to 76%.

Dioxane turned out to be the most suitable solvent.

In view of the fact that many acetylene and diacetylene esters and their derivatives exhibit bacteriocidal properties [2, 5], the synthesized aminoacetylene esters were subjected to iodomethylation and hydrohalogenation. The resultant iodomethylates and hydrochlorides (IVa-h) were crystalline substances, soluble in water, partially soluble in acetone and ethanol, and insoluble in the remaining organic solvents (Table 2).

The series dilution method in a liquid nutrient medium [1] was employed to test the bacteriocidal activity of IVa-h against saprophytes and assumed pathogenic and pathogenic bacteria. Data on bacteriocidal activity are given in Table 3.

The tested compounds were found to have a lethal effect on the typhoid pathogen when used a comparatively high concentrations. The dysentery pathogen was found to most sensitive to IV e, h, and the E. coli pathogenic serotypes were most sensitive to IVc-f.

Of the tested compounds only the iodomethylate IVg had a lethal effeet on Proteus mirabilis.

Tashkent Medical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 7, pp. 833-836, July, 1987. Original article submitted March 4, 1986.

 0091-150X/87/2107-0510$12.50

TABLE 1. Physical and Chemical Constants of Aminoacetylene Fatty Acid Esters (IIIa-h)

Compound	Yield, %	mp, °C/mm Hg	n_D^{20}	d_4^{20}	Found, %			Empirical formula	Calculated, %		
					C	H	N		C	H	N
IIIa	76	56—7/2	1,4520	0,9847	61,80	8,35	9,20	$C_9H_{13}NO_2$	61,91	8,44	9,02
IIIb	74	92—4/2	1,4534	0,9393	68,12	9,75	6,79	$C_{12}H_{21}NO_2$	68,21	10,00	6,63
IIIc	76	112—4/2	1,4546	0,9227	70,19	10,45	5,72	$C_{14}H_{25}NO_2$	70,25	10,53	5,85
IIId	75	133—6/2	1,4555	0,9144	71,68	10,67	5,34	$C_{16}H_{29}NO_2$	71,86	10,93	5,24
IIIe	73	151—3/2	1,4570	0,9072	72,87	11,15	4,64	$C_{18}H_{33}NO_2$	73,13	11,25	4,74
IIIf	72	162—4/2	1,4586	0,9015	74,17	11,25	4,53	$C_{20}H_{37}NO_2$	74,25	11,53	4,33
IIIg	74	175—7/2	1,4600	0,9012	74,81	11,56	3,78	$C_{22}H_{41}NO_2$	75,16	11,75	3,98
IIIh	74	24—6	—	—	75,40	11,45	3,51	$C_{24}H_{45}NO_2$	75,56	11,85	3,83

TABLE 2. Iodomethylates and Chlorohydrates of Aminoacetylene Fatty Acid Esters (IVa-h)

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	Cl	I		C	H	Cl	I
IVa	95,1	134—6	36,48	5,35	—	42,61	$C_9H_{16}INO_2$	36,39	5,42	—	42,72
IVb	94,0	96—8	44,12	6,70	—	35,85	$C_{13}H_{24}INO_2$	44,20	6,84	—	35,92
IVc	84,3	92—4	60,75	9,38	12,69	—	$C_{14}H_{28}ClNO_2$	60,96	9,50	12,85	—
IVd	89,5	96—8	63,05	9,80	11,78	—	$C_{16}H_{32}ClNO_2$	63,24	9,95	11,66	—
IVe	92,7	137—8	52,31	8,40	—	29,19	$C_{19}H_{36}INO_2$	52,17	9,29	—	29,01
IVf	81,8	73—5	66,89	10,79	9,95	—	$C_{20}H_{38}ClNO_2$	66,73	10,64	9,84	—
IVg	93,4	128—30	56,18	8,82	—	25,89	$C_{23}H_{44}INO_2$	55,98	8,98	—	25,71
IVh	83,8	107—9	69,15	11,03	8,68	—	$C_{24}H_{46}ClNO_2$	69,28	11,14	8,52	—

TABLE 3. Bacteriocidal Activity (minimum bacteriostatic concentrations, mg/ml) of Aminoacetylene Fatty Acid Esters (IVa-h)

Compound	S. typhi abdominalis	Sh. Flexneri	Staphylococcus pyogenes		Streptococcus			Escherichiae			Proteus		B. mycoides
			V. albus	aureus штамм 209	pyogenes v. hamoliticus	faecalis	faecalis v. zymog.	coli communis	pathogenic serotypes O55	pathogenic serotypes O111	mirabilis	morganii	
IVa	—	—	—	—	—	0,15	—	—	—	—	—	—	—
IVb	—	—	—	—	0,6	—	—	—	—	—	—	—	—
IVc	—	—	0,6	0,3	2,5	0,15	6,0	0,3	0,15	—	—	—	—
IVd	—	—	1,2	0,3	1,2	0,15	0,3	1,2	0,6	—	—	—	0,15
IVe	—	0,6	0,3	0,15	0,15	0,6	0,15	1,2	0,6	—	—	—	0,15
IVf	25,0	—	2,5	—	—	1,2	2,5	2,5	—	—	—	—	2,5
IVg	25,0	—	1,2	0,15	—	0,15	—	—	—	—	0,15	—	0,15
IVh	12,0	0,6	0,6	0,15	6,0	0,15	6,0	2,5	—	—	—	—	0,15
Streptomycin	0,2	0,3	0,2	0,3	0,1	0,2	0,3	0,4	0,6	0,6	0,6	0,5	0,2
Levomycetin	0,5	0,4	0,4	0,4	0,6	0,4	0,6	0,6	0,8	1,0	1,0	1,0	0,4

The tested preparations were inactive against Proteus morganii, but at a comparatively low concentrations exhibited a pronounced lethal effect on the B. mycoides group of microorganisms.

We observed a relationship between the antimicrobial action of the synthesized preparations and their chemical structure. Thus, we found that the compounds tended to increase their bacteriocidal activity in proportion to the size of the fatty acid hydrocarbon radical.

EXPERIMENTAL

Aminoacetylene Esters of Fatty Acids (IIIa-h). A mixture of 0.75 mole of paraformaldehyde, 0.05 mole of II, 0.05 mole of Ia-h, 0.62 g of copper acetate, and 60 ml of dioxane was heated at 100-104°C for 7 to 8 h. After cooling, 10% HCl was added to the reaction mixture which was extracted with ether. The remaining portion was made alkaline with 25% NH_4OH and extracted with ether again. The ether extracts were combined and dried, the solvent was distilled off, and the target product was obtained by vacuum distillation (see Table 1).

N-Dimethylaminobutine-2-yl-acetic Iodomethylate (IVa). A 0.02 mole of MeI in acetone was added while stirring to 0.01 mole of IIIa dissolved in 40 ml of acetone. After the stirring was stopped the mixture was slowly brought to a boil for 3 h. The acetone was then distilled off and the precipitant crystals were washed with petroleum ether, resulting in IVa.

Compounds IVb, e, and g were obtained in the same way.

N-Dimethylaminobutine-2-yl-caprylic HCl (IVc). A 0.01 mole portion of IIIc was dissolved in 30 ml of anhydrous acetone. Dry HCl was then passed into the solution until its saturation point. The solvent was evaporated and the residue was washed with ether, resulting in IVc.

Compounds IVd, f, and h (see Table 2) were obtained in the same manner.

LITERATURE CITED

1. E. A. Ved'mina and N. M. Furer, Multivolume Guide to the Microbiology, Clinical Aspects, and Epidemiology of Infectious Diseases [in Russian], Vol. 4, Moscow (1964), pp. 602-603.
2. N. P. Glazunova, L. P. Kirillova, O. G. Yashina, and L. I. Vereshchagin, Khim.-farm. Zh., No. 4, 18-23 (1974).
3. A. G. Makhsumov and M. S. Ergashev, Uzb. Khim.-farm. Zh., No. 2, 26-28 (1984).
4. A. G. Makhsumov and M. S. Ergashev, Khim.-farm. Zh., No. 7, 827-829 (1984).
5. G. N. Pershin, S. N. Milovanova, A. L. Mikerina, et al., Izv. AN SSSR, Ser. Khim., No. 8, 1904-1906 (1970).

AMINO ACIDS OF THE ADAMANTANE SERIES.

II. SYNTHESIS OF ADAMANTYL-CONTAINING AMINO ALCOHOLS FROM α-AMINO ACIDS AND THEIR ANTIVIRAL ACTIVITY

P. A. Krasutskii, I. G. Semenova,
M. I. Novikova, A. G. Yurchenko,
N. A. Leont'eva, and T. V. Veselovskaya

UDC 615.281.8:[547.435.1:547.592.1].012.1

In continuation of our studies on the antiviral activity of adamantane α-amino acid derivatives [1], a series of adamantyl-containing 1,2-amino alcohols was synthesized.

It is known that the 1,2-amino alcohol fragment is included in the composition of many physiologically active compounds [3]; at the same time, these compounds are hydroxy analogs of 2-amino-2-(1-adamantyl)ethane hydrochloride (remantadine), a preparation that has found use in medicine.

The amino alcohols VII-XIIa were obtained in high yields by reduction of methyl esters of amino acids (I-VI) by lithium aluminum hydride by the method described in [4]. The reduction of compounds I and V was carried out in dry ether, and that of compounds II-IV and VI in dry tetrahydrofuran at a molar ratio methyl ester of amino acid-lithium aluminum hydride equal to 1:4. The course of the reaction was monitored by IR spectroscopy and GLC. The excess of the reducing agent was decomposed by alkali [5]. The ether solutions of the amino alcohols VII-XII were treated with hydrogen chloride and the hydrochlorides of 2-(1-adamantyl)-, 2-(1-adamantyl-3-methyl)-, 2-(1-adamantyl-3,5-dimethyl)-, 2-(1-adamantyl-3,5,7-trimethyl)-2-aminoethanols (VIIa-Xa), the hydrochloride of 3-(1-adamantyl)-2-aminopropanol (Xa) and the hydrochloride of bis(2-aminoethanol)adamantane were isolated.

A hydrochloride of 1-(1-adamantyl)-2-chloroethylamine (XIII) was also synthesized. It is readily formed by boiling the hydrochloride of amino alcohol VIIa in thionyl chloride. This compound can be regarded as a chloro analog of remantadine, and therefore it was of interest to study its antiviral activity.

The data of the elemental analysis, yields and physical constants of the synthesized compounds are given in Table 1.

EXPERIMENTAL CHEMICAL

The IR spectra were run on a UR-10 spectrophotometer (GDR) in potassium bromide tablets. The elemental analysis was carried out on a "C, H, N-Analyzer" apparatus (CSSR).

Kiev Polytechnical Institute, Kiev. D. I. Ivanovskii Institute of Virology, Academy of Medical Sciences of the USSR.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 7, pp. 836-840, July, 1987. Original article submitted May 2, 1986.

0091-150X/87/2107-0512$12.50