RESEARCH ON UNSATURATED LACTONES.

75. ANTIVIRAL ACTIVITY OF SOME LACTONES

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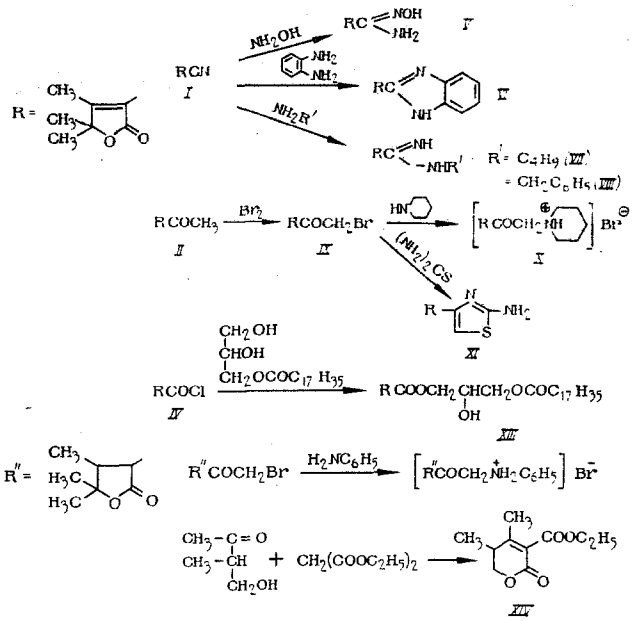
Continuing our search for biologically active compounds based on substituted lactones, we have accomplished several chemical transformations that lead to new systems that contain heterocyclic (lactone, lactam, etc) rings. Thus the reaction of 3-cyano-4,5,5-trimethyl-Δ^3-butenolide (I) with amines led to the corresponding amidines containing lactone or lactam rings (V-VIII); by the action of bromine on 3-acetyl-4,5,5-trimethyl-Δ^3-butenolide (II) we obtained the bromoacetyl derivative (IX), by reaction of which with piperidine and thiourea we obtained, respectively, the piperidine salt and a substituted thiazole, which contain unsaturated lactone rings (X, XI). The arylammonium salt with an unsaturated lactone ring (XII) was obtained by reaction of bromoacetyl-butyrolactone (III) with aniline; by reaction of the acid chloride of 3-carboxy-4,5,5-trimetyl-Δ^3-butenolide (IV) with α-monostearin we obtained the corresponding ester (XIII). We also accomplished the synthesis of 3-carbethoxy-4,5-dimethyl-5,6-dihydro-2-pyrone (XIV) by condensation of 2-acetylpropanol with malonic ester.

The indicated reactions are represented by the following schemes:



The structures of the compounds obtained were proved by the IR spectra. The purities and identities were verified by thin-layer chromatography (TLC).

EXPERIMENTAL BIOLOGICAL SECTION

The antiviral properties of the compounds were studied by the method described in [1-3]. Of the 10 investigated compounds, three (V, X, and XL) displayed activity and selectivity with

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TABLE 1. Results of Tests of Antiviral Activity

Compound	Maximally tolerable concn., μg/ml	Viruses						
		influenza	parainfluenza	VEE	ECHO	adeno	herpes	vaccines
V	100	—	—	—	—	—	++	—
VI	200	—	—	—	—	—	—	—
VII	100	—	—	—	—	—	—	—
VIII	400	—	—	—	—	—	—	—
IX	1	—	—	—	—	—	—	—
X	400	—	—	+	—	—	++	—
XI	200	—	—	++	—	—	+++	—
XII	400	—	+++	+	—	—	—	—
XIII	400	—	—	—	—	—	—	—
XIV	1	+++	—	—	—	—	—	—

Note: The dash lines indicate no effect, the plus signs indicate a virtually inactive compound, the double plus signs indicate slight antiviral activity, and the triple plus signs denote moderate antiviral activity.

respect to the herpes virus (Table 1), and of these, XI displayed an inhibiting effect also with respect to the Venezuelan equine encephalitis (VEE) virus. None of the compounds displayed any virus-inhibiting activity with respect to the ECHO viruses, adenoviruses, and vaccines. Compound XII did display an inhibiting effect with respect to the parainfluenza virus, while XIV induced supression of the formation of plaques by the influenza virus. Compounds IX and XIV proved to be toxic to chick embryo fibroblast cultures; the maximally tolerable concentration of these substances was 1 μg/ml.

EXPERIMENTAL CHEMICAL SECTION

The IR spectra of suspensions of the compounds in mineral oil were recorded with IKS-14 and UR-20 (German Democratic Republic) spectrometers. Thin-layer chromatography (TLC) was carried out on plates with a layer of L 40/100μ silica gel with development by means of iodine vapors. Compounds I, II, and IV were obtained by the methods in [4, 5].

3-Carboxy-4,5,5-trimethyl-Δ^3-butenolide Amidoxime (V). A mixture of 3.3 g (0.022 mole) of I, 1.55 g (0.02) of hydroxylamine hydrochloride, and 1.55 g (0.011 mole) of potassium carbonate in 20 ml of water and 20 ml of alcohol was stirred for 10 h at 80-82°C, after which the solvent was removed by distillation, and the residue was extracted with ether. The ether extracts were washed with water and dried over magnesium sulfate. The ether was then removed, and the product was recrystallized from alcohol (Table 2). IR spectrum (λ, cm^{-1}): 1750, 1610, 1680, 1620-1650, and 3370-3500.

3-(2-Benzimidazolyl)-4,5,5-trimethyl-Δ^3-butenolide (VI). A mixture of 6 g (0.04 mole) of I, 1.5 g (0.045 mole) of o-phenylenediamine, and 152 of phosphoric acid was stirred at 165-170°C for 5 h, after which the mixture was cooled and washed successively with water, 10% sodium carbonate solution, and water. The product was isolated by recrystallization from alcohol (see Table 2). IR spectrum (ν, cm^{-1}): 1750, 1620, 1650, 1660, 3360.

4,5,5-Trimethyl-Δ^3-crotonolactam 3-(N-Subsituted amidines) (VII, VIII). A mixture of 0.015 mole of I, 0.015 mole of butyl- or benzylamine, and 20-30 ml of absolute dioxane or benzene was refluxed for 25 h, after which the solvent was removed by distillation, and the residue was subjected to vacuum distillation. IR spectrum (ν, cm^{-1}): 1705, 1575, and 3473.

3-Bromoacetyl-4,5,5-trimethyl-Δ^3-butenolide (IX). A solution of 6.5 ml of bromine in 5-6 ml of chloroform was added dropwise with stirring and gentle heating to a solution of 16.8 g (0.1 mole) of II in 40 ml of chloroform, after which the mixture was allowed to stand at room temperature for 3-4 h. The solvent was then removed, and the residue was distilled *in vacuo* (see Table 2). IR spectrum (ν, cm^{-1}): 1750, 1705, and 1590.

3-Bromoacetyl-4,5,5-trimethylbutyrolactone (III). This compound was similarly obtained in 90% yield and had bp 145-7°C (2 mm). Found, %: C 43.79, H 5.41, Br 31.90. $C_9H_{13}BrO_3$. Calculated, %: C 43.37, H 5.22, Br 32.12. IR spectrum (ν cm^{-1}): 1770, 1710.

TABLE 2. Characteristics of the Compounds Obtained

Compound	Yield, %	°C	R_f	Found					Empirical formula	Calc., %				
				C	H	N	Br	S		C	H	N	Br	S
V	70,0	142—3	0,55	52,35	6,94	15,22	—	—	$C_8H_{12}N_2O_3$	52,17	6,52	15,22	—	—
VI	95,0	220	0,72	69,81	6,05	12,00	—	—	$C_{14}H_{14}N_2O_2$	69,42	5,78	11,57	—	—
VII	16,1	129—30	9,60	60,70	9,10	13,26	—	—	$C_{16}H_{29}N_3O$	69,90	8,73	13,58	—	—
VIII	69,5	235—7	0,70	76,42	7,29	12,67	—	—	$C_{22}H_{25}N_3O$	76,36	7,23	12,30	—	—
IX	90,0	166—8	0,63	44,10	4,81	—	32,65	—	$C_8H_{11}BrO_3$	43,72	4,45	—	32,38	—
X	42,0	188—90	0,68	50,32	6,35	4,65	24,00	—	$C_{14}H_{22}BrNO_3$	50,60	6,62	4,21	24,10	—
XI	75,2	145—7	0,58	34,04	4,81	12,70	—	14,44	$C_{10}H_{12}N_2O_2S$	53,81	4,93	12,55	—	14,29
XII	43,0	180—2	0,81	52,26	5,52	4,45	23,41	—	$C_{15}H_{20}BrNO_3$	52,63	5,84	4,09	23,32	—
XIII	53,0	76—7	0,66	68,01	9,99	—	—	—	$C_{29}H_{50}O_7$	68,24	9,80	—	—	—
XIV	30,3	158—160	0,75	60,49	7,12	—	—	—	$C_{10}H_{14}O_4$	60,60	7,07	—	—	—

Note: The boiling points at 1.5 mm (mercury column) are indicated for VII, VIII, and IX.

3-(Piperidinoacetyl)-4,5,5-trimethyl-Δ^3-butenolide and 3-(Anilinoacetyl)-4,5,5-trimethylbutyrolactone Hydrobromides (X, XII). A 0.15-mole sample of the appropriate amine (piperidine, aniline) was added dropwise to a solution of 0.015 mole of bromoacetyl lactone IX or III, and the mixture was allowed to stand at room temperature for 1-2 h. The solvent was then removed by distillation, and the residue was washed with ether and recrystallized (see Table 2).

3-(2-Amino-4-thiazolyl)-4,5,5-trimethyl-Δ^3-butenolide (XI). A solution of 4.5 g (0.02 mole) of IX in 10 ml of alcohol was added dropwise to a mixture of 1.5 g (0.02 mole) of thiourea and 25 ml of alcohol, after which the mixture was stirred for 4-5 h. The solvent was then removed by distillation, and the residue was washed with water, neutralized with ammonium hydroxide, and washed again with ether (see Table 2). IR spectrum (ν, cm^{-1}): 1750, 1620, 3370-3480.

3-Carbo-(2-hydroxy-3-stearyloxy)propyloxy-4,5,5-trimethyl-Δ^3-butenolide (XIII). A solution of 1.3 g (0.0067 mole) of IV in 4 ml of benzene was added to a mixture of 2.4 g (0.0067 mole) of α-monostearate, 2 ml of absolute benzene, and 3 ml of pyridine, after which the mixture was refluxed for 5 h. The solvent was then removed by distillation, and the residue was recrystallized from ethyl acetate (see Table 2). IR spectrum (ν, cm^{-1}): 1766, 1710, 1650, 3295-3385.

3-Carbethoxy-4,5-dimethyl-5,6-dihydro-2-pyrone (XIV). A mixture of 10.2 g (0.1 mole) of 2-acetylpropanol, 16.8 g (0.11 mole) of malonic ester, and 13.8 g (0.1 mole) of potassium carbonate was stirred at 150-160°C for 30-32 h. The extracts were then dried over magnesium sulfate, and the solvent was removed; the residue was distilled *in vacuo* (see Table 2). IR spectrum (ν, cm^{-1}): 1720, 1700, 1620.

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