UNSATURATED LACTONES.

LXXIII. SYNTHESIS AND ANTIVIRAL ACTIVITY OF SOME SUBSTITUTED 2-BUTEN-4-OLIDES

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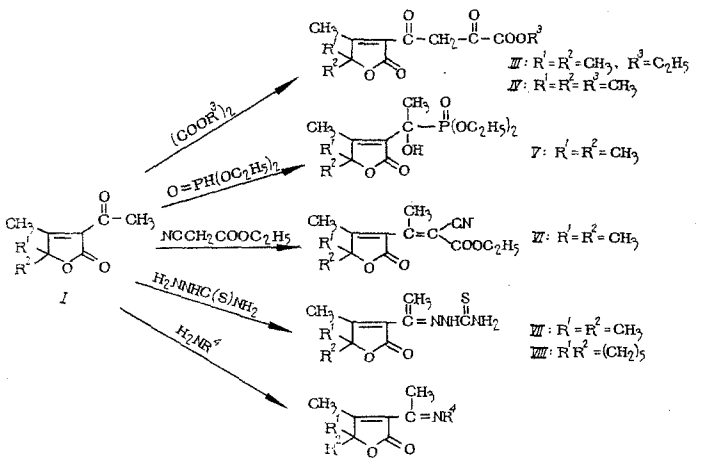
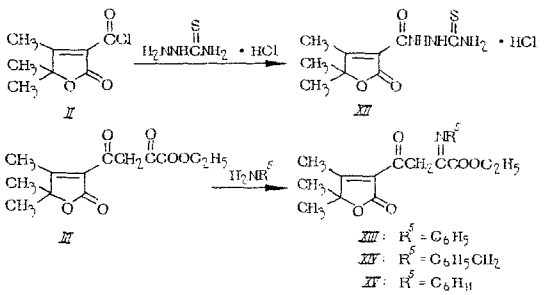
It is known [1-11] that compounds (both synthetic, and of natural origin) containing the lactone ring possess quite a wide spectrum of biological activity. Methods have been developed [12-16] for the preparation of substituted 2-buten-4-olides with a variety of functional substituents. In order to obtain new compounds containing the 2-buten-4-olide ring and to examine their antiviral activity, we have carried out some chemical reactions of 2-acyl derivatives of 2-buten-4-olides (I-III), in which the lactone ring is conserved, as follows:





The starting 2-acetyl-2-buten-4-olides (I) and 3,4,4-trimethyl-2-buten-4-olide-2-carbonyl chlorides (II) were obtained by previously-described methods [13, 17].

The structures of the compounds obtained were confirmed by spectral analyses, and their purity by TLC. Molecular masses were determined by mass spectrometry.

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TABLE 1. 2-Buten-4-olides

Compound	Yield, %	mp, °C	R_f	Found, %						Molecular formula	Calculated, %					
				C	H	N	Cl	P	S		C	H	N	Cl	P	S
III	84,4	96—8	0,82	58,40	6,40	—	—	—	—	$C_{13}H_{16}O_6$	58,21	5,95	—	—	—	—
IV	54,3	38—40	0,62	56,32	5,62	—	—	—	—	$C_{12}H_{14}O_6$	56,69	5,51	—	—	—	—
V	46,0	84	0,88	51,00	7,11	—	—	10,56	—	$C_{13}H_{23}O_6P$	50,98	7,52	—	—	10,13	—
VI	81,0	76—7	0,74	64,20	6,12	5,51	—	—	—	$C_{14}H_{17}NO_4$	63,88	6,46	5,32	—	—	—
VII	93,0	184—6	0,57	50,21	6,50	17,43	—	—	13,41	$C_{10}H_{15}N_3O_2S$	49,79	6,22	17,43	—	—	13,28
VIII	92,9	210—2	0,61	55,86	6,43	14,72	—	—	11,54	$C_{13}H_{19}N_3O_2S$	55,52	6,76	14,95	—	—	11,39
IX	54,4	190—2	0,67	68,55	7,98	7,00	—	—	—	$C_{22}H_{30}N_2O_4$	68,39	7,77	7,25	—	—	—
X	32,6	159,60	0,72	60,00	6,22	7,60	—	—	—	$C_{18}H_{22}N_2O_6$	59,67	6,08	7,73	—	—	—
XI	42,1	165—6	0,66	55,73	5,48	9,02	—	—	10,15	$C_{15}H_{18}N_2O_4S$	55,90	5,59	8,70	—	—	9,94
XII	73,5	168—70	0,80	38,44	4,89	15,14	12,91	—	11,67	$C_9H_{14}N_3ClO_3S$	38,64	5,01	15,03	12,70	—	11,45
XIII	60,0	162—4	0,65	66,64	6,0	3,99	—	—	—	$C_{19}H_{21}NO_5$	66,48	6,12	414	—	—	—
XIV	59,8	135—6	0,55	64,50	6,29	4,00	—	—	—	$C_{20}H_{23}NO_5$	64,43	6,16	3,92	—	—	—
XV	75,2	140—1	0,57	65,13	7,56	4,19	—	—	—	$C_{19}H_{27}NO_3$	65,33	7,74	4,01	—	—	—

EXPERIMENTAL CHEMICAL SECTION

IR spectra were obtained on a UR-20 spectrophotometer (East Germany), in vaseline oil, PMR spectra on Hitachi (Japan) and Perkin-Elmer R-20B (Sweden) instruments with a working frequency of 60 MHz, internal standard HMDS, and mass spectra on an MX-1303 instrument with direct introduction of the sample into the ion source. TLC was carried out on Silufol, visualization by iodine vapor.

2-(1'Alkoxycarbonyl-1',3'-dioxopropyl)-3,4,4-trimethyl-2-buten-4-olides (III, IV). To a solution of 6 g (0.036 mole) of (I) ($R^1 = R^2 = CH_3$) in 14.6 g (0.1 mole) of diethyl oxalate, or (I) and 4.25 g (0.036 mole) of dimethyl oxalate in 20 ml of dry methanol was added with stirring 4 g (0.074 mole) of dry sodium methoxide. The mixture was heated at 60-80°C for 11-12 h, and following removal of the solvent in the second case (without removal in the first case), it was treated with 300 ml of 3% acetic acid. The resulting precipitate was filtered off, washed with water, acidified with acetic acid, and recrystallized from light petroleum (Table 1). IR spectrum, ν, cm^{-1}: 1750 (lactone C=O), 1720 (ester C=O), 1690 (ketone C=O), 1620 (C=O).

Diethyl 1-(3',4',4'-Trimethyl-2'-buten-4'-olidyl)-1-hydroxyethyl-1-phosphonate (V). To a mixture of 4.2 g (0.025 mole) of (I) ($R^1 = R^2 = CH_3$) and 3.45 g (0.025 mole) of diethyl phosphate was added 3-4 drops of diethylamine, and the mixture kept at room temperature until crystals ceased to separate. These were then filtered off and recrystallized from ether (see Table 1). IR spectrum, ν, cm^{-1}: 1740 (C=O), 1650 (C=C), 1221-56 (P=O), 982-8 and 1058-86 (POC), and 3313-20 (OH).

2-(2'-Ethoxycarbonyl-2'-cyano-1'-methylethenyl)-3,4,4-trimethyl-2-buten-4-olide (VI). A mixture of 4 g (0.024 mole) of (I) ($R^1 = R^2 = CH_3$), 2.7 g (0.024 mole) of cyanoacetic ester, 0.09 g of β-alanine, 2.5 ml of glacial acetic acid, and 20 ml of dry benzene was boiled until all the water had been removed in a water separator (15-17 h). The solution was decanted or filtered from the solid, the solvent removed from the filtrate, the residue distilled *in vacuo* (boiling point 185-187°C at 3 mm), and recrystallized from ether (see Table 1). IR spectrum, ν, cm^{-1}: 1754 (lactone C=O), 1728 (ester C=O), 1604 (C=C), 2240 (CN). PMR spectrum, ppm: 2.08 s, 1.53 s, 1.50 s (3- and 4-ring CH_3), 2.55 s, 2.45 s (trans- and cis-side chain CH_3), 1.36 s (ester CH_3), and 4.28 m (ester CH_2).

2-Acetyl-2-buten-4-olide Thiosemicarbazones (VII, VIII). A mixture of 25 g (0.023 mole) of thiosemicarbazide hydrochloride and 50 ml of alcohol was boiled for 30 min, followed while heating was continued by the dropwise addition of a solution of 0.023 mole of the appropriate (I) in 25 ml of alcohol. Boiling was continued for a further 6-8 h, and the mixture then kept at room temperature until separation of the crystalline precipitate was complete. This was then filtered off and recrystallized from benzene (see Table 1). IR spectrum, ν, cm^{-1}: 1745-50 (C=O), 1654-55 (C=N), 1465 (C=S), 3250-3365 (NH_2). Molecular masses: found 241 (VII), and 281 (VIII); calculated 241.31 (VII) and 281.39 (VIII).

2-(1'-Iminoethyl)-3,4,4-trimethyl-2-buten-4-olides (IX-XI). A mixture of 2 g (0.012 mole) of (I) ($R^1 = R^2 = CH_3$) with 3.1 g (0.012 mole) of 4-(N,N-diethylaminoethoxycarbonyl)-aniline hydrochloride, and 0.55 g of sodium in absolute ethanol, or with 0.012 mole of 1-(4'-nitrophenyl)-2-amino-1,3-propanediol or 4-aminosulfonylaniline in 10 ml of glacial acetic acid was boiled for 4 h, then treated with water and the crystals which separated crystallized respectively from hexane, benzene, or acetone (see Table 1). IR spectrum, ν, cm^{-1}: 1745-1750 (lactone C=O), 1715 [ester C=O for (IX)], 1654-62 (C=N), 1580-1600 (benzene), 1380 [NO_2 for (X)], 3250-3365 [NH_2 for (XI)], 3270 [HO for (X)]. Molecular masses: found 386 (IX), 362 (X), 322 (XI); calculated 386.50 (IX), 362.39 (X), 322.39 (XI).

2-Carboxy-3,4,4-trimethyl-2-buten-4-olide Thiosemicarbazide Hydrochloride (XII). A mixture of 1 g (0.0052 mole) of (II) and 0.5 g (0.0052 mole) of thiosemicarbazide in 10 ml of DMF was heated for 5-6 h at 95-96°C. After cooling, 5 ml of concentrated hydrochloric acid was added, the solvent removed, and the residue recrystallized from a mixture of alcohol and benzene (1:1) (see Table 1). IR spectrum, ν, cm^{-1}: 1745 (lactone C=O), 1685 (amide C=O), 3265-3340 (NH_2).

2-(1-Ethoxycarbonyl-1-imino-3-oxopropyl)-3,4,4-trimethyl-2-buten-4-olides (XIII-XV). A mixture of 2 g (0.007 mole) of (III) and 0.007 mole of the appropriate amide in 15-20 ml of alcohol was heated for 8-10 h at 40-50°C, filtered, the solvent removed from the filtrate, and the residue recrystallized from hexane (see Table 1). IR spectrum, ν, cm^{-1}: 1740-50

TABLE 2. Results of Tests for Antiviral Activity in the Compounds Prepared

Compound	Maximum tolerated concentration, μg/ml	Test virus						
		influenza	parainfluenza	VEE	ECHO	adeno	herpes	vaccines
III	50	NT	—	—	—	—	—	—
IV	2.5	NT	—	—	—	—	—	—
V	10	NT	—	—	—	—	—	—
VI	50	NT	—	—	—	—	—	—
VII	100	—	—	—	—	—	—	—
VIII	400	—	—	—	—	—	—	—
IX	25	—	—	—	—	—	—	—
X	25	—	—	+	—	—	—	—
XI	400	—	—	—	—	—	—	—
XII	100	+++	—	—	—	—	+++	—
XIII	10	—	—	—	—	—	—	—
XIV	25	—	—	—	—	—	—	—
XV	100	—	—	—	—	—	—	—

Note. (—) indicates no effect, (++) slight antiviral activity, (+++) moderate antiviral activity, NT not tested.

(lactone C=O), 1710-25 (ester C=O), 1695-1700 (ketone C=O), 1610-20 (C=C), 1750-55 (C=N). Molecular masses: found 343 (XIII), 357 (XIV), 349 (XV); calculated 343.39 (XIII), 357.41 (XIV), 349.43 (XV).

EXPERIMENTAL BIOLOGICAL SECTION

The antiviral activity of the compounds synthesized was determined with respect to the viruses influenza A (FPV) Rostock/34 (HavlN1), type 3 parainfluenza, Venezuelan equine encephalomyelitis (VEE-230), type 3 adeno-virus, ECHO type 6, herpes simplex C1, and vaccines. Primary trypsinized cultures of chick embryo fibroplasts were examined. The antiviral properties of the compounds were assessed by the occurrence of suppression of the cytopathogenic effects of viruses cultured in the presence of nontoxic doses of the compounds, and their antiviral activities were estimated by the methods described in detail in [18-20].

The compounds possessed varying degrees of toxicity towards chick embryo fibroplast cultures, the maximum tolerated concentrations lying within the range 2.5-400 μg/ml.

The results obtained (Table 2) show that most of the compounds were inactive towards the test viruses. Compound (X) was weakly active towards VEE virus, and (XII) had a weak inhibitory effect on influenza virus. The latter compound also possessed antiviral activity against herpes virus.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF β-(N-CYCLOHEXAMETHYLENEAMINO)ETHYL ESTERS OF DICARBOXYLIC ACIDS

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A study of the literature [1] on the relationship between structure and pharmacological activity of amino esters (dicarboxylic acid derivatives) shows that the size, composition, and structure of the alkyl radical between the nitrogen atoms accounts for the activity of the compounds.

Studies conducted earlier [2] have shown that the methiodides of β-dimethylaminoethyl esters of dicarboxylic acids I show different (curare-like or analeptic) pharmacological activity depending upon the number of methylene groups in the acid portion of the molecule. The maximum curare-like and analeptic activities were enhanced at n = 2 and n = 6, respectively. Subsequently, for clarification of the significance of the alkyl radicals on

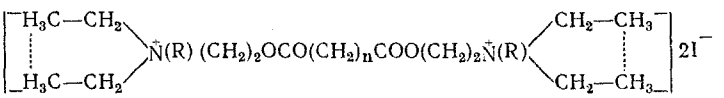
$$[(CH_3)_3\overset{+}{N}-(CH_2)_2OCO-(CH_2)_n-COO(CH_2)_2-\overset{+}{N}(CH_3)_3]\,2I^-$$
I

the nitrogen atoms, the methyl groups were successively replaced by ethyl (II); specifically, the curare-like compound Dithiline (I, n = 2) was obtained. This showed that all of the compounds IIa, b, c (n = 2) were less active than I (n = 2), by as

$$[RR'R''\overset{+}{N}-(CH_2)_2OCO-(CH_2)_n-COO(CH_2)_2-\overset{+}{N}RR'R'']\,2I^-$$
II

IIa: $R = C_2H_5$, $R' = R'' = CH_3$; IIb: $R = C_2H_5$, $R' = C_2H_5$, $R'' = CH_3$;
IIc: $R = R' = R'' = C_2H_5$.

much as 100 times. The following study leads to a more exact definition of the significance of geometry (conformation) for the activity of these molecules. For this purpose, the rotation of the terminal carbon atom joining the two ethyl groups was restricted (III), resulting in derivatives of pyrrolidine. As was shown in a phar-



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