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SYNTHESIS AND CYTOTOXIC ACTIVITY OF 4-SUBSTITUTED 3-CYANO-6,6-DIMETHYL-5,6-DIHYDRO-2-PYRANONES

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The respective 4-(arylvinyl)lactones and compounds of the Michael adduct type were synthesized by the condensation of substituted benzaldehydes with 3-cyano-4,6,6-trimethyl-5,6-dihydro-2-pyranone in the presence of catalytic amounts of sodium hydroxide. It was shown by the semiempirical AM1 method that the indicated products can be formed through one and the same intermediate compound. Some of the synthesized phenylvinyl-5,6-dihydro-2-pyranones have a cytotoxic effect, and this corresponds to the prognosis of the OREX expert system.

Keywords: benzaldehyde, substituted δ-lactones, crotonic condensation mechanism, semiempirical AM1 method, cytotoxic activity, OREX expert system.

We have shown that the reaction of methyl-substituted γ- and δ-lactones with pyridinecarbaldehydes takes place by a nontraditional mechanism, in which the products from the reaction of one molecule of the aldehyde with two molecules of the pyranone are formed in addition to the products from crotonic condensation [1]. At the same time no departures from the classical mechanism of crotonic condensation were found in [2, 3], devoted to the condensation of benzaldehyde with the above-mentioned lactones,

The aim of the present work was to investigate the condensation of 3-cyano-4,6,6-trimethyl-5,6-dihydro-2-pyranone (**1**) with substituted benzaldehydes **2**-**10** in greater detail and to determine the effect of the electronic structure of the aldehyde on the ratio of the two paths of condensation with the CH acid.

Earlier we showed that 3-cyano-6,6-dimethyl-4-[2-(4-nitrophenyl)vinyl]-5,6-dihydro-2-pyranone, like its analogs with pyridyl-containing substituents, have clearly defined cardiovascular activity [1]. The second aim of the work was therefore to analyze the potential biological activity of the synthesized compounds using the OREX system (optimized recognizing expert system), developed at the Latvian Institute of Organic Synthesis, and also to verify experimentally the established structure–activity relation.

The reaction of the aldehydes **2**-**10** with the pyranone **1** was carried out in ethanol in the presence of catalytic amounts of sodium hydroxide with the pyranone, aldehyde, and sodium hydroxide in molar ratios of (0.7-2):1:(0.06-0.13). The initial concentration was 1.87 M for the pyranone and 0.93 M for the aldehydes. According to the data in Table 1, two types of compounds (the products of crotonic condensation **11**-**19** and compounds of the Michael adduct type **20**-**28**) are formed as a result of the reaction of all the aldehydes with the pyranone **1**, and the times at which they appear and the yields depend on the nature of the substituent of the aldehyde and on the temperature.

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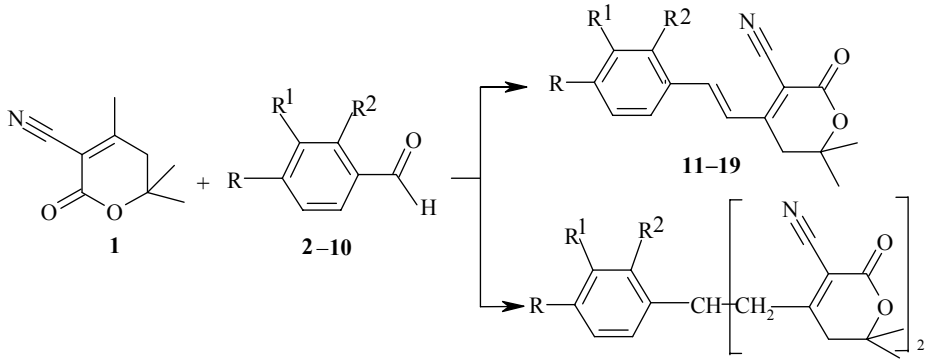
To compare the reactivity of the benzaldehydes with various substituents the yields of the reaction products were determined by HPLC without isolation from the reaction mixture. The dynamics of the process were monitored by TLC.

As seen from Table 1, in the reaction of the unsubstituted aldehyde **2** with pyranone a product of the Michael adduct type **20** is formed preferentially irrespective of the reaction temperature and the molar ratio of the reagents. The yield of this compound increases with increase in the amount of the catalyst and the reaction time. The appearance of the crotonic condensation product **11** was only observed after 4 h.



2, 11, 20 R = R^1 = R^2 = H; **3, 12, 21** R = NO_2, R^1 = R^2 = H; **4, 13, 22** R = Cl, R^1=R^2 = H;
5, 14, 23 R = Cl, R^1 = H, R^2 = Cl; **6, 15, 24** R = NMe_2, R^1 = R^2 = H;
7, 16, 25 R = Me, R^1 = R^2 = H; **8, 17, 26** R = OH, R^1 = R^2 = H;
9, 18, 27 R = OMe, R^1 = R^2 = H; **10, 19, 28** R = OH, R^1 = OMe, R^2 = H

It was not possible to isolate the products from the reaction of the pyranone **1** and the aldehyde **8**. However, to judge from the data from chromatography and from the ^{1}H NMR spectrum two compounds **17** and **26** are formed. With the pyranone and aldehyde **3** in a ratio of 2:1 compound **21** is mainly formed. However, on account of the effect of the electron-withdrawing substituent NO_2 the yield is lower than in the case of the unsubstituted aldehyde. Only if the molar ratio of the aldehyde and pyranone is 1.5:1 can the product of the Michael adduct type no longer be detected in the reaction products.

In the case of the electron-donating substituent NMe_2 (aldehyde **6**), as expected, the reaction rate is greatly reduced, and more than 76% of the pyranone remains unreacted even after keeping the reaction mixture for 4 h. The yield of the product **24** in this case is only 1.7%.

The structure of the obtained lactones was proved on the basis of the ^{1}H NMR spectra (Tables 2 and 3).

According to the ^{1}H NMR spectra, the vinyl fragment of compounds **11-16**, **18**, and **19** has the *trans* configuration (^3J = 15.9-16.2 Hz).

Comparison of the changes in the chemical shifts of the two vinyl protons with replacement of the substituent in the phenyl ring provides grounds for assigning the downfield doublet to the absorption of the proton at the C atom attached to the phenyl group (range of variation of the chemical shifts $\Delta\delta$ = 0.42 ppm), while the upfield doublet is assigned to the absorption of the proton at the C atom attached to the pyranone residue ($\Delta\delta$ = 0.26 ppm).

Attention is drawn to the fact in the spectra of the lactones **11-16**, **18**, and **19** the protons the of CH_2 and the protons of the two methyl groups in the pyranone ring are magnetically equivalent, whereas in the lactones **20-28** the chemical shifts of the same protons differ (0.04-0.16 and 0.02-0.17 ppm respectively). Dreiding models show that the pyranone ring has the form of a distorted *half-chair* and the rate of the conformational transitions changes with replacement of the substituent at position 2 of the pyranone. Magnetic nonequivalence is also observed for the CH_2 protons of the $-CH(CH_2)_2-$ fragments of compounds **20-28** (^2J = 12.4-13.2 Hz). This may be due to the considerable size of the substituted pyranones, which prevents free rotation about the CH_2–pyranone bond.

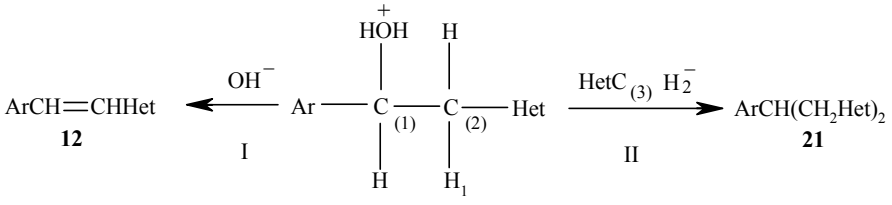
TABLE 1. Reaction of the Pyranone **1** with Benzaldehydes **2-10** at 78°C

Aldehyde	Aldehyde–pyranone–NaOH molar ratio	Time, h	Yield of reaction products, %	
			Crotonic condensation	Adduct of Michael reaction type
2	1 : 1 : 0.06	2.5*	—	63.5
2	1 : 2 : 0.06	1	—	41.5
2	1 : 2 : 0.06	4	3.1*[2]	57.6*[3]
2	1 : 2 : 0.13	4	—	81.4
3	1 : 2 : 0.06	4	22.6*[4]	75.3*[5]
3	1 : 0.7 : 0.06	4	60.0	—
4	1 : 2 : 0.06	4	15.2	52.7
5	1 : 2 : 0.06	4	33.3	52.0
6	1 : 2 : 0.06	4	11.7*[6]	1.7*[7]
7	1 : 2 : 0.06	0.1	10.9	22.7
8	1 : 2 : 0.06	0.5	24.6	21.7
9	1 : 2 : 0.06	1	14.8	39.8
10	1 : 2 : 0.06	0.5	37.9	13.2

* Reaction temperature 20°C.
*[2] Formed after 4 h.
*[3] Formed 15 min after mixing of the reagents.
*[4] Formed at moment the reagents were mixed.
*[5] Formed after 5 min.
*[6] Formed after 1 h.
*[7] Formed after 3 h.

According to our views about the mechanism of the crotonic condensation of pyridinecarbaldehydes with furanone, the two products from the reaction of benzaldehydes with pyranone **1** can be formed through one and the same intermediate product of aldol condensation type **A**, and the probable source of the protons is hydrated sodium cations [3].

In the present the model condensation of the pyranone **1** with the aldehyde **3** was studied by the semiempirical quantum-chemical AM1 method [4]. The JMol software [5] was used for visualization and animation of the obtained results, and the ChemCraft 1.3 software package [6] was used to create a design of the reaction system. It was assumed that by analogy with the reaction of pyridinecarbaldehydes the reaction of pyranone and the aldehyde **3** will take place in two directions depending on the nature of the attacking nucleophile:



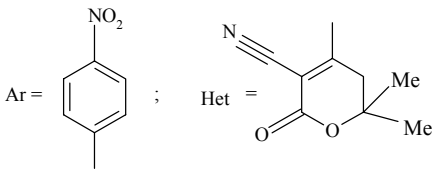


TABLE 2. The ^{1}H NMR Spectra of the Lactones **11-16**, **18**, and **19**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz)
		C	H	N		
11	$C_{16}H_{15}NO_2$	75.87 / 75.87	5.97 / 5.97	5.54 / 5.53	144-146	1.52 (6H, s, CH_3 pyranone); 2.87 (2H, s, CH_2 pyranone); 7.29 and 7.45 (2H, d and d, *J* = 16.2, CH=CH); 7.3-7.7 (5H, m, C_6H_5)
12	$C_{16}H_{14}N_2O_4$	64.40 / 64.42	4.67 / 4.73	9.35 / 9.39	224-226	1.55 (6H, s, CH_3 pyranone); 2.88 (2H, s, CH_2 pyranone); 7.31 and 7.54 (2H, d and d, *J* = 16.2, CH=CH); 7.76 (2H, m, *J* = 9.0, C_6H_4 H_2, H_6); 8.3 (2H, m, *J* = 9.0, C_6H_4 H_3, H_5)
13	$C_{16}H_{14}ClNO_2$	66.74 / 66.79	4.84 / 4.90	4.88 / 4.87	180-182	1.53 (6H, s, CH_3 pyranone); 2.86 (2H, s, CH_2 pyranone); 7.25 and 7.46 (2H, d and d, *J* = 16.1, CH=CH); 7.42 (2H, m, *J* = 8.9, C_6H_3 H_2, H_6); 7.55 (2H, m, *J* = 8.9, C_6H_4 H_3, H_5)
14	$C_{16}H_{13}Cl_2NO_2$	59.69 / 59.65	4.06 / 4.07	4.29 / 4.35	212-214	1.55 (6H, s, CH_3 pyranone); 2.88 2H, s, CH_2 pyranone); 7.34 1H, dd, *J* = 8.6 and 2.0, C_6H_3 H_5) 7.38 and 7.63 (2H, d and d, *J* = 16.2, CH=CH); 7.47 (1H, d, *J* = 2.0, C_6H_3 H_3); 7.74 (1H, d, *J* = 8.6, C_6H_3 H_6)
15	$C_{18}H_{20}N_2O_2$	72.88 / 72.95	6.75 / 6.80	9.40 / 9.45	192-194	1.50 (6H, s, CH_3 pyranone); 2.81 (2H, s, CH_2 pyranone); 3.08 (6H, s, $N(CH_3)_2$; 6.68 (2H, m, *J* = 9.0, C_6H_4 H_2, H_6); 7.22 (2H, s, CH=CH); 7.51 (2H, m, *J* = 9.0, C_6H_4 H_3, H_5)
16	$C_{17}H_{17}NO_2$	76.36 / 76.38	6.40 / 6.41	5.26 / 5.24	143-145	1.52 (6H, s, CH_3 pyranone); 2.40 (3H, s, $CH_3C_6H_4$); 2.85 (2H, s, CH_2 pyranone); 7.24 (2H, m, *J* = 8.2, C_6H_4 H_3, H_5), 7.26 and 7.39 (2H, d and d, *J* = 15.6, CH=CH); 7.51 (2H, m, *J* = 8.2, C_6H_4 H_2, H_6)
18	$C_{17}H_{17}NO_3$	72.06 / 72.07	6.06 / 6.05	4.93 / 4.94	139-141	1.51 (6H, s, CH_3 pyranone); 2.84 (2H, s, CH_2 pyranone); 3.87 (3H, s, OCH_3); 6.95 (2H, m, *J* = 8.9, C_6H_4 H_2, H_6); 7.25 and 7.31 (2H, d and d, *J* = 15.9, CH=CH); 7.58 (2H, m, *J* = 8.9, C_6H_4 H_3, H_5)
19	$C_{17}H_{17}NO_4$	68.19 / 68.22	5.72 / 5.72	4.66 / 4.68	233-236 (dec.)	1.42 (6H, s, CH_3 pyranone); 3.09 (2H, s, CH_2 pyranone); 3.84 (3H, s, OCH_3); 6.89 (1H, d, *J* = 7.8, C_6H_3 H_5); 7.12 and 7.64 (2H, d and d, *J* = 15.9, CH=CH); 7.2-7.4 (2H, m, C_6H_3 H_2, H_6); 10.0 (1H, s, OH)

TABLE 3. The Characteristics of the Lactones

Compound	Empirical formula	Found, % / Calculated, % C	H	N	mp, °C	^{1}H NMR (DMSO-d_6), δ, ppm (*J*, Hz)
20	$C_{25}H_{26}N_2O_4$	71.72 / 71.75	6.26 / 6.26	6.70 / 6.69	188-192	1.23 and 1.25 (12H, s and s, CH_3 of pyranone); 2.33 and 2.49 (4H, d and d, *J* = 18.9, CH_2 of pyranone); 3.00 (2H, dd, *J* = 12.4 and 10.4 $CH(CH_2)_2$; 3.09 (2H, dd, *J* = 12.4 and 5.6 $CH(CH_2)_2$; 3.49 (1H, m, CH); 7.2-7.5 (5H, m, C_6H_5)
21	$C_{25}H_{25}N_3O_6$	64.65 / 64.79	5.42 / 5.44	9.03 / 9.07	204-207 (dec.)	1.22 and 1.35 (12H, s and s, CH_3 of pyranone); 2.75 and 2.80 (4H, d and d, CH_2 of pyranone); 3.02 and 3.08 (4H, m and m, $CH(CH_2)_2$; 3.71 (1H, m, CH); 7.68 2H, m, *J* = 9.6, C_6H_4 H_2 and H_6); 8.18 (2H, m, *J* = 9.6, C_6H_4 H_3, H_5)
22	$C_{25}H_{25}ClN_2O_4$	66.27 / 66.30	5.57 / 5.56	6.14 / 6.18	183-185 (dec.)	1.18 and 1.32 (12H, s and s, CH_3 of pyranone); 2.75 and 2.81 (4H, d and d, CH_2 of pyranone); 3.00 and 3.04 (4H, m and m, $CH(CH_2)_2$; 3.51 (1H, m, CH); 7.40 (4H, s, C_6H_4)
23	$C_{25}H_{24}Cl_2N_2O_4$	61.63 / 61.61	4.87 / 4.96	5.69 / 5.75	212-214	1.23 and 1.30 (12H, s and s, CH_3 of pyranone); 2.73 and 2.77 (4H, d and d, CH_2 of pyranone); 3.05 and 3.11 (4H, m and m, CH $(CH_2)_2$; 3.97 (1H, m, CH); 7.4-7.8 (3H, m, C_6H_3)
25	$C_{26}H_{28}N_2O_4$	72.16 / 72.20	6.52 / 6.53	6.47 / 6.48	185-187	1.16 and 1.33 (12H, s and s, CH_3 of pyranone); 2.25 (3H, s, $C\underline{H}_3C_6H_4$); 2.73 and 2.82 (4H, d and d, *J* = 19.1, CH_2 of pyranone); 2.95 and 3.04 (4H, m and m, $CH(CH_2)_2$; 3.50 1H C_6H_4 (1H, m, CH); 7.12 (2H, m, *J* = 7.8, C_6H_4 H_2, H_6); 7.22 (2H, m, *J* = 7.8, C_6H_4 H_3, H_5)
26	$C_{25}H_{26}N_2O_5 \cdot 0.5\ H_2O$	67.76 / 67.71	6.18 / 6.14	6.26 / 6.32	157-160 (dec.)	1.16 and 1.31 (12H, s and s, CH_3 of pyranone); 2.72 and 2.79 (4H, d and d, CH_2 of pyranone); 2.8-3.1 (4H, m, $CH(CH_2)_2$; 3.35 (1H, m, CH); 6.68 (2H, m, *J* = 8.5, C_6H_4 H_2, H_6); 7.14 (2H, m, *J* = 8.5, C_6H_4 H_3, H_5); 9.37 (1H, s, OH)
27	$C_{26}H_{28}N_2O_5$	69.54 / 69.63	6.24 / 6.29	6.30 / 6.25	193-196 (dec.)	1.16 and 1.32 (12H, s and s, CH_3 of pyranone); 2.72 and 2.83 (2H, d and d, *J* = 19.2, CH_2 of pyranone); 2.95 and 3.03 (4H, m and m, $CH(CH_2)_2$; 3.50 (1H, m, CH); 3.71 (3H, s, OCH_3); 6.87 (2H, m, *J* = 8.6, C_6H_4 H_2, H_6); 7.26 (2H, m, *J* = 8.6, C_6H_4 H_3, H_5)
28	$C_{26}H_{28}N_2O_6 \cdot 0.5\ C_2H_5OH \cdot 0.5\ H_2O$	65.55 / 65.31	6.31 / 6.50	5.63 / 5.64	158-160 (dec.)	1.23 and 1.33 (12H, s and s, CH_3 of pyranone); 2.70 and 2.86 (4H, d and d, *J* = 19.1, CH_2 of pyranone); 3.10 (2H, dd, *J* = 13.2 and 5.6, $CH(CH_2)_2$; 3.23 (2H, dd, *J* = 13.2 and 10.0, $CH(CH_2)_2$; 3.57 (1H, m, CH); 3.90 (3H, s, OCH_3); 6.72 (1H, d, *J* = 8.0, C_6H_3 H_5); 6.78 (1H, dd, *J* = 8.0 and 1.8, C_6H_3 H_6); 7.10 (1H, d, *J* = 1.8, C_6H_3 H_2); 7.71 (1H, s, OH)

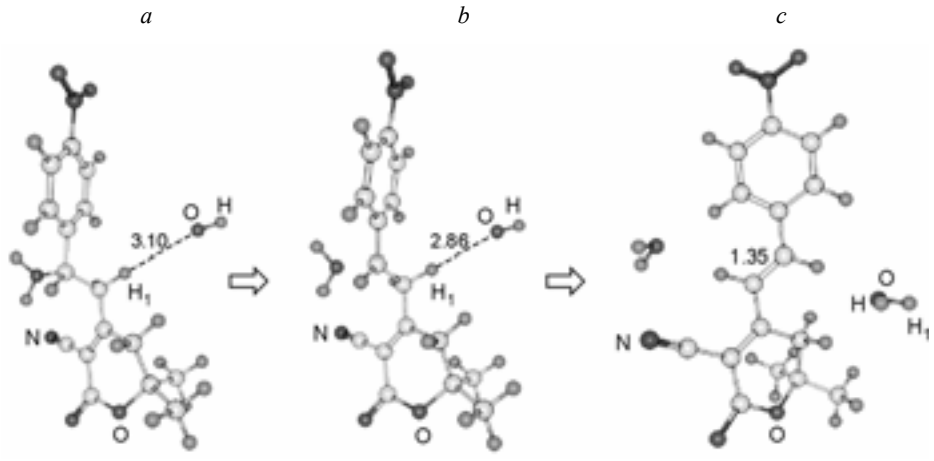


Fig. 1. Reaction of the intermediate compound **A** with the OH^- ion:
a) the starting position; b) elimination of the H_2O molecule; c) the reaction products.

Thus, the reaction of the intermediate **A** with the OH^- ion can lead to the product from crotonic condensation **12**. At the starting position the OH^- ion is on an extension of the $C_{(2)}$–$H_{(1)}$ bond at a distance of 3.10 Å from the $H_{(1)}$ atom (Fig. 1a).

If this distance is reduced to 2.86 Å a molecule of water is eliminated from the $C_{(1)}$ atom. Subsequently, the $H_{(1)}$ atom is removed from the $C_{(2)}$ atom by the action of the OH^- ion, and this leads to the formation of another molecule of water and the product **12** (Fig. 1c). Thus, this reaction path is realized by an *E2* mechanism. The length of the double bond in compound **12** of 1.35 Å corresponds to data in [7]. The calculations show that the reaction takes place spontaneously without an energy barrier. The enthalpy of this reaction is -1011.7 kJ/mol.

Figure 2a shows the selected starting position during calculation of the reaction system containing the intermediate compound **A** and the ion $HetC_{(3)}H_2^-$. The $C_{(3)}$–$C_{(1)}$ and $C_{(3)}$–$H_{(1)}$ distances are 5.14 and 3.30 Å respectively. The $HetC_{(3)}H_2^-$ ion, in which the $C_{(3)}$ atom is negatively charged (-0.386), attacks the positively

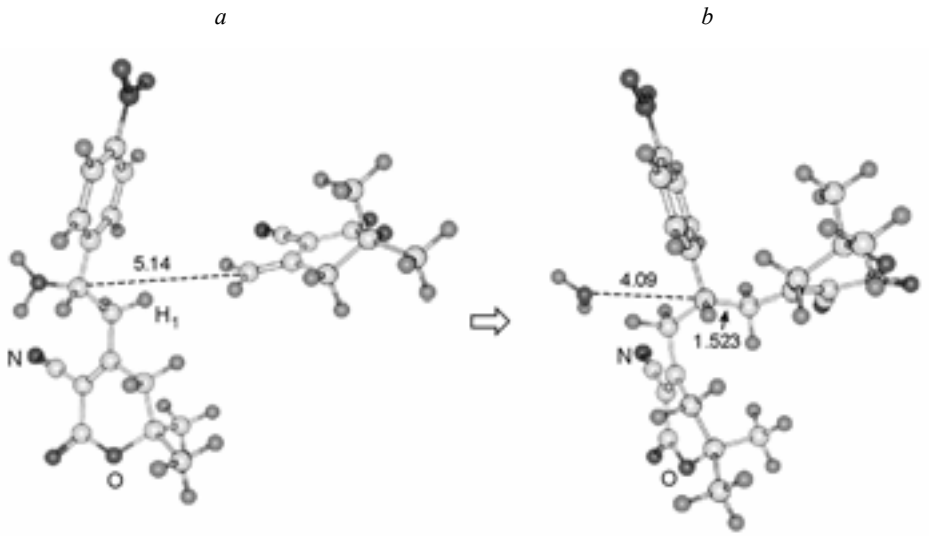


Fig. 2. Reaction of the intermediate product **A** and the ion $HetCH_2^-$:
a) the initial state; b) the reaction products (compound **21** and a water molecule).

charged $C_{(1)}$ atom (0.146) of the intermediate compound **A**. When the $C_{(3)}$–$C_{(1)}$ distance decreases to 4.89 Å, a molecule of water is eliminated from the $C_{(1)}$ atom. Further decrease of the distance between the $C_{(3)}$ and $C_{(1)}$ atoms to 1.523 Å leads to the formation of compound (**21**) (Fig. 2b). At this moment the distance between the water molecule and the $C_{(1)}$ atom amounts to 4.09 Å. During visualization of the process it is possible to see how gradual Walden inversion of the configuration at the $C_{(1)}$ atom occurs in the course of the reaction. The calculations show that the reaction of the $HetC_{(3)}H_2^-$ ion with the intermediate **A** takes place spontaneously without the need to overcome an energy barrier. The heat of this reaction amounts to -697.1 kJ/mol.

Earlier it was shown by calculation that reaction of deprotonated at methyl group furanone with an intermediate compound takes place regioselectively during the condensation of 3-cyano-4,5,5-trimethyl-2(5H)-furanone with 3-pyridinecarbaldehyde [3]. Thus, if attack by the indicated anion was directed at the $C_{(1)}$ atom of the intermediate compound (having a structure similar to compound **A** in the present work), bimolecular nucleophilic substitution (S_N2) occurred, resulting in the formation of a product of the Michael adduct type. At the same time the ethenyl derivative of furanone and the initial furanone are formed as a result of attack at the $H_{(1)}$ atom, i.e., an $E2$ bimolecular elimination reaction occurs.

As follows from the results of the quantum-chemical analysis, in the case of the reaction of the pyranone **1** with the aldehyde **3** in the reaction of the intermediate compound **A** with the deprotonated pyranone only the product of the Michael adduct type is formed, irrespective of the direction of attack by the anion. This may explain the fact that the yield of the product **21** under similar conditions is higher that the yield of the compound of the same type produced by the reaction of 3-cyano-4,5,5-trimethyl-2(5H)-furanone with 3-pyridinecarbaldehyde (81.5 and 59.5% respectively).

Thus, the results of the present work indicate that the reactions of δ- and γ-methyllactones with aryl and hetaryl aldehydes are fairly general in nature and involve the formation not only of the crotonic condensation product but also a product of the Michael adduct type.

The OREX expert system [8, 9] was used to predict the biological activity of the synthesized compounds. OREX is a system of programs for the creation and analysis of a data base and knowledge base and also for predicting biological activity. The algorithms of the logic-structural approach are based on the selection and subsequent incorporation of reliable indicators of biological activity, i.e., the structural fragments that determine the type of biological activity. The description of the chemical structure was based on descriptor centers and graphs representing the topology of the molecule. The program codes the structure of the compounds on the basis of the descriptor centers, singling out descriptors that are in the final count an abstract representation of the structure. The activity indicators are selected from the set of descriptors according to the working rules of a system of the following type:

$$f \xrightarrow{P} A$$

if the compound has indicator ***f***, it will then exhibit activity ***A*** with probability ***P***.

The indicators are selected according to their statistical value, determined in the data base employed as statistical sample. During screening of the compounds that we synthesized in the OREX program it was shown that the phenylvinyl derivative of the γ-lactone may have anticancer activity. It is possible to state with some degree of probability that the mechanism of their action involves the inhibition of RNA synthesis and also necrosis of the tumor in the respective systems (Fig. 3).

The cytotoxic activity of the synthesized compounds on a monolayer strain of tumor cells MG-22A (mouse hepatoma) and their ability to stimulate the biosynthesis of nitric oxide radicals (NO·), one of the possible components of the cytotoxic effect, were tested on the basis of the prediction results (Table 4). The strongest cytotoxic effect is exhibited by the nitrophenylvinyl and chlorophenyl derivatives of pyranone (compounds **12** and **13**), which at low concentrations (5 and 6 μg/ml) secure the destruction of cells of the MG-22A line. The pyranone **13** is characterized by a high level of generation of NO· in the cells (800%, coloration CV), which may explain its high cardiovascular activity [1].

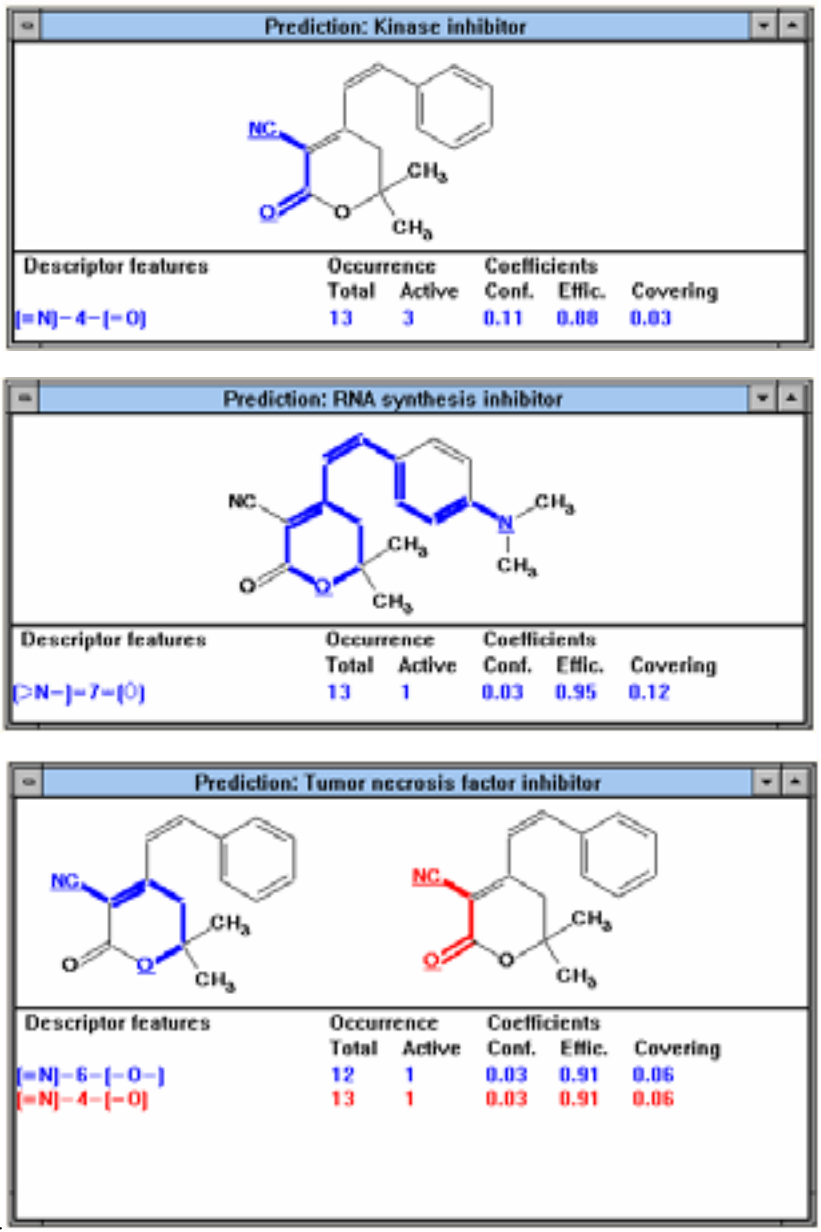


Fig. 3. Prediction of the activity in OREX.

Total is the total amount of the compounds containing the given descriptor in the data base;
Active is the number of active compounds containing the given descriptor in the data base;
Conf. is the confidence coefficient, indicating the lowest level of probability with which the compound possessing the given activity indicator actually exhibits this activity;
Effic. is the coefficient of efficiency, indicating by how many times the compound possessing this indicator has a higher probability of exhibiting the given activity than any compound taken at random;
Covering is the covering coefficient and shows what part of the active compounds possesses a given indicator.

TABLE 4. The Biological Effect of Phenyllactones (*in vitro*) on a Monolayer Culture of MG-22A

Compound	Cytotoxicity, μg/ml*		Generation of NO· (100% CV)
	TD_{50} (CV)	TD_{50} (MTT)	
11	26	48	67
12	5	33	21
13	6	17	800
14	58	75	17
15	*[2]	*[2]	5
16	28	42	50
18	34	32	50
19	*[2]	*[2]	6
20	*[2]	*[2]	9
22	52	58	300
23	*[2]	*[2]	15
25	55	74	53
26	*[2]	*[2]	11
27	*[2]	*[2]	9
28	*[2]	*[2]	7

* TD_{50} is the concentration securing 50% destruction of cells, μg/ml; CV is coloration with crystal violet; MTT is coloration with 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide [10, 11]; the nitric oxide was determined by Grace's method in the culture medium a over cells and converted to 100% live cells with coloration by CV [10].

*[2] There was no cytotoxic effect.

EXPERIMENTAL

The yield of the reaction products was determined by HPLC on a Nova-Pak Silica column (3.9 × 150 mm). The delivery rate of the eluant (1:1 ethyl acetate–hexane) was 1.5 ml/min, UV detector, 254 nm. The ^{1}H NMR spectra were recorded on a Mercury 200B instrument (200 MHz) in deuterochloroform and DMSO-d_6 with TMS as internal standard. TLC was conducted on Silufol UV-254 plates with 1:1 ethyl acetate–hexane as eluant.

The quantum-chemical calculations were carried out by the semiempirical AM1 method using MOPAC 6 software with full optimization of the geometry of the reagents, reaction system, and reaction products in the EF regime at the PRECISE level.

Condensation of 3-Cyano-4,6,6-trimethyl-5,6-dihydro-2-pyranone with Benzaldehyde (General Procedure). A mixture of pyranone **1**, aldehyde **2-10**, and sodium hydroxide in ethanol was heated with stirring to boiling and boiled for 4 h or kept at room temperature. The product of the Michael adduct type that separated was filtered off without cooling the mixture. After cooling to room temperature the ethenyl derivative of the lactone was filtered off. Both products were purified by recrystallization from ethanol.

The enthalpy of reaction was calculated as the difference between the total energy of the final state of the system and the sum of the total energies of the isolated reagents – the anion (OH^- or $HetC_{(3)}H_2^-$) and the intermediate.

Additional information on the changes in geometry during the reaction can be obtained on request from the authors (e-mail: misha@osi.lv).

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