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SYNTHESIS AND BIOLOGICAL ACTIVITY OF α-ALKYLACROLEIN DIMERS AND THEIR DERIVATIVES

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Dimers of methacrolein and α-ethylacrolein have been obtained and undergo a Cannizzaro reaction to the corresponding pyran alcohols and sodium salts of pyran acids. Their bacteriostatic, bactericidal, and fungicidal properties have been studied.

Keywords: 2,5-dimethyl-3,4-dihydro-2H-pyran-2-carbaldehyde, 2,5-dimethyl-3,4-dihydro-2H-pyran-2-methanol, 2,5-diethyl-3,4-dihydro-2H-pyran-2-carbaldehyde, 2,5-diethyl-3,4-dihydro-2H-pyran-2-methanol, sodium salts of 2,5-dimethyl-3,4-dihydro-2H-pyran-2-carboxylic and 2,5-diethyl-3,4-dihydro-2H-pyran-2-carboxylic acids, Diels-Alder reaction, Cannizzaro reaction.

Dimers of α-alkylacroleins can be prepared by a Diels-Alder reaction [1, 2] and also as side products in the synthesis of α-alkylacroleins due to their thermal dimerization [3, 4]. Despite the widespread use of a diene synthesis for the preparation of various carbo- and heterocyclic compounds the α-alkylacrolein dimers belong to a class of rather poorly studied compounds – pyrans. Literature data regarding methods of synthesis, properties, and areas of use for the pyrans are limited [5-7] and refer mainly to acrolein and methacrolein dimers.

In the example of the dimerization of α-alkylacroleins one molecule of the aldehyde is the diene and the other the dienophile and this leads to the formation of a product with a dihydropyran ring with two reactive centers, *viz*. the –C=C– and carbaldehyde group. Due to the presence of a carbonyl group in the dimer molecule it is possible to introduce different substituents containing double bonds, hydroxyl, carbonyl, carboxyl, amino, cyano, and other groups and hence to obtain novel materials having a broad range of practical use [8]. Dimer derivatives, in turn, attract the attention of investigators because compounds with different properties can be created on their basis. There is evidence in the literature that both the α-alkylacrolein dimers themselves and their derivatives have quite high bactericidal, bacteriostatic, antiviral, and antifungal activities. Hence the acrolein dimer is used as starting material in the preparation of the antibiotics kanamycin, astromicin, and negamycin [9, 10] and the methacrolein dimer and derivatives as starting materials for preparing insect repellents and active insecticides [11, 12].

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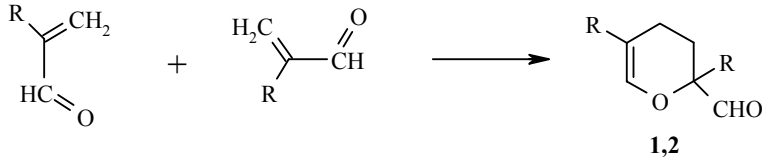
The challenge of creating medicinal compounds, plant growth regulators, insecticides, and herbicides is very current and demands a growth in research in the areas of synthesis and studies of novel pyran compounds [13-15]. Literature data basically relates only to the synthesis, reactions, and uses of the dimers of acrolein and methacrolein. In order to widen the range of novel compounds relating to the accumulation of a database for the dependence of a Diels-Alder reaction for α-alkylacroleins we have studied the dimerization process of α-ethylacrolein and its behavior in the Cannizzaro reaction.

For conversion to the dimer of the next acrolein homolog member (α-ethylacrolein) it was necessary to use more rigid conditions. Thanks to the lower tendency to polymerization of α-ethylacrolein than acrolein it is a more suitable subject for studying the kinetic dependence of the dimerization reaction in α-alkylacroleins which is virtually unknown in the literature. According to a preceding publication [16] the nature and state of the substituent in the diene system affects the rate of the diene reactions. The presence of electron donor substituent groups in the diene molecule increases its reactivity while electron acceptor groups makes it less active. In addition, an increase in the alkyl radical at position 2 of the pyran ring confers novel properties on the compound prepared.

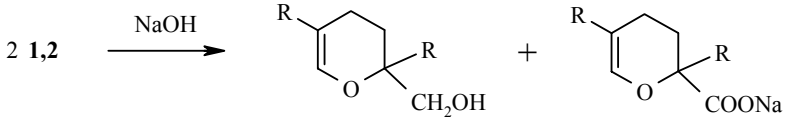
Diels-Alder reactions using methacrolein (R = Me) and α-ethylacrolein (R = Et) as starting materials gave the dimers 2,5-dimethyl-3,4-dihydro-2H-pyran-2-carbaldehyde (**1**) and 2,5-diethyl-3,4-dihydro-2H-pyran-2-carbaldehyde (**2**).



1,2

1 R = Me, **2** R = Et

The dimers **1** and **2** then underwent a Cannizzaro reaction to give the corresponding 2,5-dimethyl-3,4-dihydro-2H-pyran-2-methanol (**3**), 2,5-diethyl-3,4-dihydro-2H-pyran-2-methanol (**4**), and the sodium salts of the 2,5-dimethyl-3,4-dihydro-2H-pyran-2-carboxylic (**5**) and 2,5-diethyl-3,4-dihydro-2H-pyran-2-carboxylic acids (**6**).



3, 4 **5, 6**

1, 3, 5 R = Me; **2, 4, 6** R = Et

Table 1 shows the results of a study of the bactericidal action of the compounds investigated. The data obtained shows that compound **4** has bactericidal properties towards Gram-positive and -negative microorganisms but only towards gram positive microorganisms for compounds **2** and **3**, while in compound **1** this activity is less marked.

Table 2 shows the results of a study of the fungicidal activity of the compounds prepared. It was found that compounds **2** and **4** have fungicidal activity towards *Candida albicans, Aspergillus fumigatus, and Penicillium chrysogenum*.

It was also found that compounds **2** and **3** show a bacteriostatic effect on the Gram-positive organisms *Staphylococcus aureus 209 and Streptococcus*. Compound **4** shows weak bacteriostatic activity towards gram positives (*Staphylococcus aureus 209, Streptococcus*) and Gram-negatives (*Escherichia coli, Salmonella enteritidis*) and the dimer **1** on Gram-positives (*Staphylococcus aureus 209, Streptococcus*).

According to these results the dimers **1** and **2** show bacteriostatic and bactericidal activity towards the indicated materials. An increase in the alkyl radical at position 2 of the pyran ring gave an increase in activity, dimer **2** proving more active than dimer **1** while the dimer **1** showed no fungicidal action.

The exchange of the pyran carbonyl group in **1** for an alcohol in compound **3** leads to activation of the bacteriostatic and bactericidal effect in the molecule. In the case of compounds **2** and **4** a reverse effect occurs, i.e. an increase in the alkyl radical causes a lowering of both bacteriostatic and bactericidal activity in compound **4** although, at the same time, it proved to be a good fungicide.

TABLE 1. Results of the Bactericidal Activity of the α-Alkylacrolein Dimers and their Derivatives*

Compound	Diameter of the zone of growth inhibition, mm			
	Escherichia coli	*Salmonella enteritidis*	*Staphylococcus aureus 209*	*Streptococcus*
1	0	0	12	15
2	0	0	30	25
3	0	0	24	25
4	12	15	18	20

* c = 10000 μg / disc.

TABLE 2. Results of the Fungicidal Activity of the α-Alkylacrolein Dimers and their Derivatives*

Compound	Diameter of the zone of growth inhibition, mm		
	Candida albicans	*Aspergillus fumigatus*	*Penicillium chrysogenum*
1	0	0	0
2	15	13	13
3	0	0	0
4	13	11	10
Pimafucin control	15	15	15

* c = 1000 μg / disc.

TABLE 3. Results of the Bacteriostatic Activity of the α-Alkylacrolein Dimers and their Derivatives*

Compound	Diameter of the zone of growth inhibition, mm			
	Escherichia coli	*Salmonella enteritidis*	*Staphylococcus aureus 209*	*Streptococcus*
1	0	0	12	15
2	0	0	20	20
3	0	0	24	25
4	15	18	18	19
Control	18*[2]	18*[2]	24*[3]	24*[3]

* c = 1000 μg / disc.
*[2] Amikacin.
*[3] Ciprofloxacin.

EXPERIMENTAL

The study of the bacteriostatic, bactericidal, and fungicidal properties of the compounds synthesized was carried out according to the following methods.

The bacteriostatic and bactericidal activities towards Gram-negative and Gram-positive cultures were determined by the diffusion method in agar with the use of paper discs with the investigated compounds in the culture medium in order to determine the sensitivity of the microorganisms towards the antibiotics and also by serial dilution according to the method [17].

Fungicidal activity for the synthesized compounds was determined using a Saburaud medium. The dish with culture medium was inoculated with *Candida albicans, Aspergillus fumigatus, or Penicillium chrysogenum*. The paper discs were sterilized and impregnated with the investigated samples, dried off, and applied to the inoculated disk with Saburaud medium. A standard disc with the antifungal preparation pimafucin served as the control. The diameter of the inhibition of growth around the disc with the inoculated sample was compared with the control after 24-48 h incubation.

IR spectra for the synthesized compounds were recorded on a Specord M-80 spectrometer as a thin film in KBr cuvets (d = 0.024 mm). ^{1}H NMR spectra were recorded on a Varian XL-400 spectrometer (400 MHz) using $CDCl_3$ with TMS as internal standard.

Monitoring of the course of the synthesis of the dimers and their derivatives was carried out by GLC on a GCHF 18.3 instrument using computational recording of the analytical signal. Chromatographic conditions: DTP detector, detector current 140 mA, stainless steel column of length 2 m and diameter 4 mm filled with 3% XE-60 on Chromaton N Super (0.16-0.20 mm), column temperature 145ºC, detector temperature 185ºC, evaporator temperature 200ºC, and hydrogen gas carrier flow 25 ml/min.

2,5-Dimethyl-3,4-dihydro-2H-pyran-2-carbaldehyde (1). Chromatographically pure α-methylacrolein was synthesized by a Mannich reaction [18] and used in the dimerization. The methacrolein dimerization was carried out in glass, thermostatted ampules of volume 10-20 ml by the following method. Hydroquinone (0.1%) was added to the aldehyde (50 ml, 0.603 mol) and equal amounts were placed in ten ampules, purged with nitrogen, and sealed. The sealed ampules were placed in a thermostat at 170ºC and held for 2 h. The synthesized dimer **1** was vacuum fractionated. Yield 86.6%. Bp 34ºC (5 mm Hg), d_4^{20} = 0.9917, n_D^{20} = 1.4538. IR spectrum (thin film), ν, cm^{-1}: 3068, 2960-2840 (C–H), 1740 (C=O), 1668 (C=C), 1150–1070 (C–O). Found, %: C 68.45; H 8.6. $C_8H_{12}O_2$. Calculated, %: C 68.50; H 8.55.

2,5-Diethyl-3,4-dihydro-2H-pyran-2-carbaldehyde (2). Chromatographically pure α-ethylacrolein was synthesized *via* a Mannich reaction [18]. Dimerization was carried out by the method reported above for 2 h at 190ºC. The synthesized dimer **2** was vacuum fractionated. Yield 87.1%. Bp 93-94ºC (12 mm Hg), d_4^{20} = 0.9794, n_D^{20} = 1.4614. IR spectrum (thin film), ν, cm^{-1}: 3068, 2960-2840 (C–H), 1740 (C=O), 1668 (C=C), 1150-1170 (C–O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 0.916 (3H, t, J = 7.2, CH_3); 0.94 (3H, t, J = 7.2, CH_3); 1.75-2.06 (8H, m, $2CH_2$ ring, $2CH_3$–C<u>H$_2$</u>–); 6.37 (1H, s, =CH–O–); 9.54 (1H, s, –CHO). Found, %: C 74.80; H 8.40. $C_{10}H_{16}O_2$. Calculated, %: C 74.92; H 8.33.

Sodium Salt of 2,5-Dimethyl-3,4-dihydro-2H-pyran-2-carboxylic Acid (5) and 2,5-Dimethyl-3,4-dihydro-2H-pyran-2-methanol (3). A 40% aqueous solution of NaOH (7.3 ml, 0.1 mol) was added dropwise over 30 min at 40°C to a glass reactor charged with the methylacrolein dimer (29.2 g, 0.21 mol). At the end of the reaction the viscous, homogeneous mass was treated with water (35 ml) and transferred to a separating funnel. 2,5-Dimethyl-3,4-dihydro-2H-pyran-2-methanol was extracted from the reaction mixture using portions of diethyl ether (25 ml). Water was distilled from the aqueous fraction under vacuum to give compound **5** (17.3 g, 0.097 mol) which decomposed at 190ºC. Yield 93%. Found, %: C 53.79; H 6.11. $C_8H_{11}NaO_3$. Calculated, %: C 53.93; H 6.22.

The ether extract was fractionated to give compound **3** (13.6 g, 0.096 mol). Yield 92%. Bp 93-94ºC (12 mm Hg), d_4^{20} = 1.0160, n_D^{20} = 1.4750. IR spectrum (thin film), ν, cm^{-1}: 3064, 2960-2840 (C–H), 3610 (O–H), 1672 (C=C), 1200-1000 (C–O). Found, %: C 67.53; H 9.90. $C_8H_{14}O_2$. Calculated, %: C 68.02; H 9.92.

Sodium Salt of 2,5-Diethyl-3,4-dihydro-2H-pyran-2-carboxylic Acid (6) and 2,5-Diethyl-3,4-dihydro-2H-pyran-2-methanol (4) were prepared by the method described for compounds **5** and **3**. The Na salt **6** decomposes at 190ºC. Yield 83%. ^{1}H NMR spectrum (in D_2O), δ, ppm (*J*, Hz): 0.907 (3H, t, *J* = 7.2, CH_3); 0.98 (3H, t, *J* = 7.2, CH_3); 1.67-2.17 (8H, m, $2CH_2$ ring, $2CH_3$–C<u>H</u>$_2$–); 6.25 (1H, s, =CH–O–). Found, %: C 58.12; H 7.18. $C_{10}H_{15}NaO_3$. Calculated, %: C 58.24; H 7.33.

Compound 4. Yield 82%. Bp 83-85ºC (1 mm Hg), d_4^{20} = 0.9946, n_D^{20} = 1.4768. IR spectrum (thin film): 3064, 2960-2840 (C–H), 3610 (O–H), 1672 (C=C), 1200-1000 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.857 (3H, t, *J* = 7.2, CH_3); 0.969 (3H, t, *J* = 7.2, CH_3); 1.50-1.90 (8H, mm, $2CH_2$ ring, $2CH_3$–C<u>H</u>$_2$–); 6.122 (1H, s, =CH–O–); 4.140 (1H, s, OH); 3.527 (2H, s, C<u>H</u>$_2$–OH). Found, %: C 71.09; H 10.10. $C_{10}H_{18}O_2$. Calculated, %: C 70.55; H 10.66.

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