BENZOXAZOLINONES.

IV. REACTION OF BENZOXAZOLINONE AND BENZOXAZOLINETHIONE WITH ALKYL β-CHLOROVINYL KETONES

R. G. Aflyatunova, N. A. Aliev,
Ch. Sh. Kadyrov, and M. R. Yagudaev

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The reactions of benzoxazolinone and benzoxazolinethione with alkyl β-chlorovinyl ketones have been studied. The reaction products are N-(β-acylvinyl)benzoxazolinones and N-(β-acylvinyl)benzoxazolinethiones. The reaction of alkali-metal salts of benzoxazolinone with alkyl β-chlorovinyl ketones leads to the opening of the oxazolinone ring. The structures of the compounds synthesized have been studied by IR, mass, and PMR spectroscopy.

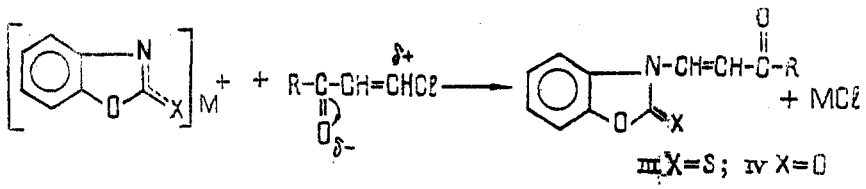
Many benzoxazolinone derivatives that are products of plant origin possess various biological activities [1, 2]. Continuing a systematic investigation in the field of benzoxazolinone and its analogs, we have studied the ketovinylation reaction. According to the literature, benzoxazolinone and its metal salts form products at the nitrogen atom with alkylating and acylating agents [2].

Alkyl chlorovinyl ketones are extremely reactive electrophilic compounds, containing in their molecule a mobile chlorine atom, a multiple carbon–carbon bond, and also a carbonyl group. In spite of this, they react with many nucleophilic reagents through the chlorine atom [3].

On studying the reactions of benzoxazolinone (I) and benzoxazolinethione (II) with alkyl chlorovinyl ketones, we found that both in the presence of triethylamine and when the reactions were carried out with aqueous solutions of their alkaline metal salts, products substituted at the nitrogen atom (λ_{max} 300-310 nm) were formed. The formation of N-(β-acylvinyl)-benzoxazolinethiones confirms the well-known fact that alkyl β-chlorovinyl ketones are vinylogs of carboxylic acid chlorides [4]. As is known [5], with benzoxazolinethione the latter give N-acetylated products [6].

Thus, because of the positive charge on one of its carbon atoms, an alkyl chlorovinyl ketone reacts with the ambident anion of benzoxazolinethione at the atom with the highest electron density, i.e., at the hard center of the ambident anion.

In the case of reactions of anions of benzoxazolinone, the final products are N-(β-acylvinyl)benzoxazolinones (IV).



III X=S; IV X=O

The reaction of (I) and (II) with an equimolecular amount of methyl, chloromethyl, ethyl, propyl, butyl, valeryl, or isovaleryl β-chlorovinyl ketone and triethylamine in benzene solution (method A) gave the corresponding N-(β-acylvinyl)benzoxazolinethione (III) or N-(β-acylvinyl)benzoxazolinone (IV), the yields of which amounted to 16-62% of theory.

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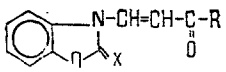
The reaction of benzoxazolinone salts with isobutyl β-chlorovinyl ketone gave a product (V) with M^+ 219:

$$2\text{—HO—}C_6H_4\text{—NH—CH=CH—COR.}$$

The presence in the IR spectrum of (V) of absorption bands corresponding to the vibrations of OH groups in the 3260-3150 and 2700-2600 cm^{-1} region due to intramolecular hydrogen bonds, at 1640 cm^{-1} as $\nu_{C=O}$ of a ketovinyl group, and also the presence in the PMR spectrum of signals of the protons of a gem-dimethyl group at (δ, ppm) 1.1 (6 H, d, J = 7 Hz) and 2.2 (CH_3—CH—CH_3, 1 H, m), at 2.35 (—CH_2—CH=CH—, m), and at 5.35 and 7.53 of cis-vinyl protons (1 H each, d 8.5 Hz) makes it possible to assume that the reaction of salts of (I) with alkyl β-chlorovinyl ketones takes place with the opening of the oxazoline ring and the formation of alkyl o-hydroxyphenylaminovinyl ketones. In its physical and spectral characteristics, product (V) differs from N-isovalerylbenzoxazolinone (VI), which also has M^+ 219 (see Experimental). The presence of a hydroxy group in compound (V) was confirmed by the reaction with $FeCl_3$ solution. Product (V) was obtained by independent synthesis starting from o-aminophenol and isobutyl β-chlorovinyl ketone

$$2\text{—HO—}C_6H_4\text{—}NH_2 + Cl\text{—CH=CHCOC}_4H_9 \xrightarrow{TEA} V\ (R = \text{iso-}\ C_4H_9).$$

The properties of the compounds synthesized are given below:



R	X	mp. °C	R_f	Yield, %
$(CH_3)_2CHCH_2$	S	108—110	0.9	17 (method B)
$(CH_3)_2CHCH_2$	S	108—110	0.9	30 (method A)
$(CH_3)_2CHCH_2$	O	91—93	0.8	30 (B)
$CH_3(CH_2)_3$	S	81—83	0.9	62 (A)
$CH_3(CH_2)_3$	O	74—75	0.81	30 (A)
$CH_3CH_2CH_2$	S	85—87	0.9	54 (A)
$CH_3CH_2CH_2$	O	95—97	0.9	22 (A)
CH_3CH_2	S	98—100	0.76	62 (B)
CH_3CH_2	O	132—134	0.83	16 (A)
CH_3	S	136—138	0.77	45 (A)
CH_2Cl	S	101—103	0.85	41 (A)

As we see, with benzoxazolinethione the yields of products are higher than with benzoxazolinone. The IR spectra of the products obtained have absorption bands in the 1670-1700 cm^{-1} region corresponding to $\nu_{C=O}$ of a ketovinyl group, and in the 930-970 cm^{-1} region to the C—H deformation vibrations of a trans-vinyl group. The carbonyl group characteristic for benzoxazolinone gives absorption in the 1780-1800 cm^{-1} region [7]. (The spectral characteristics of each of the compounds obtained are given in the Experimental part.)

It has been established that the reactions of aqueous solutions of alkali-metal salts of (I) and (II) (method B) with alkyl β-chlorovinyl ketones give far lower yields of products (III) and (IV) than method A.

In some cases, dry sodium salts of (I) and (II) prepared from metallic sodium in ethanol were also ketovinylated (method C). However, they did not give better results than method A.

It must be mentioned that on the opening of the oxazoline ring the trans configuration of the atoms of the vinyl group changes to cis. According to PMR spectroscopy, $J_{CH=CH}$ decreases to 9-10 Hz, and in the IR spectrum the trans band of nonplanar deformation vibrations of CH groups in the 970-980 cm^{-1} region disappears.

The compounds synthesized exhibited a weak fungicidal activity.

EXPERIMENTAL

IR spectra were taken on a UR-20 spectrophotometer (KBr tablets), UV spectra on a Hitachi FPS-3T spectrometer (with ethanol as solvent), mass spectra on MKh-1303 and MKh-1310 instruments, and PMR spectra on a FNM-C-60-HL spectrometer with a working frequency of 60 MHz in CCl_4 (δ scale, 0 — HMDS). The purity of the compound synthesized was monitored in a fixed layer of silica gel (Silufol) in the benzene-ethanol (21:2) system with a visualizing agent consisting of 48 ml of H_2O + 0.5 g of $KMnO_4$ + 2 ml of conc. H_2SO_4. The analyses of all the compounds agreed with the calculated figures. The benzoxazolinone and benzoxazolinethione that had not reacted were isolated by treatment with 2% aqueous alkali.

N-(β-Valerylvinyl)benzoxazolinethione (III; R = C_4H_9). A. To 3.02 g of (II) were added 2.02 g of triethylamine (TEA) and 50 ml of absolute benzene. With stirring, 2.9 g of n-butyl β-chlorovinyl ketone was added dropwise, and the mixture was stirred at room temperature for 2 h and was then heated in the water bath (at 50-60°C) for 2 h. The precipitate of TEA hydrochloride was filtered off. The benzene solution was precipitated with petroleum ether. This gave 3.25 g of (III), $C_{14}H_{15}NO_2S$, R_f 0.9, mp 81-83°C (petroleum ether); yield 62%. UV spectrum: λ_{max} 310 nm (log ε 4.79). PMR spectrum (ppm): 0.95 (CH_3, 3 H, t); 1.5 (2 CH_2, 4 H, m); 2.47 (CH_2CO, 2 H, t); 6.6 and 8.2 (CH=CH, 1 H each, d, J = 10 Hz); 7.01-7.7 (Ar–H, 4 H, m). Mass spectrum: m/z 261 (M^+), 218, 204, 186, 177, 144.

B. To 3.02 g of (II) were added 1.12 g of KOH in 30 ml of water and, with stirring, 2.9 g of n-butyl β-chlorovinyl ketone in 30 ml of acetone, and the mixture was stirred at room temperature for 2 h and was heated in the water bath (50-60°C) for 2 h. The acetone was driven off and the precipitate of (III) was filtered off; yield 54%.

N-(β-Valerylvinyl)benzoxazolinone (IV; R = C_4H_9). A. Similarly, 2.7 g of (I), 2.02 g of TEA, and 2.9 g of n-butyl β-chlorovinyl ketone yielded 1.5 g (30%) of (IV), $C_{14}H_{15}NO_3$, R_f 0.81, mp 74-75°C (petroleum ether). PMR spectrum (ppm): 0.9 (CH_3, 3 H, t); 1.45 (2 CH_2, 4 H, m); 2.5 (CH_2–CO, 2 H, t); 6.9 and 7.7 (CH=CH, 1 H each, J = 15 Hz); 7.1-7.5 (Ar–H, 4 H, m). IR spectrum: 1800 cm^{-1}, $\nu_{C=O}$ (oxazolinone ring); 1690 cm^{-1} (C=O of a ketovinyl group); 970 cm^{-1} (deformation vibrations of a trans double bond). Mass spectrum m/z 245 (M^+), 204, 187, 135, 116.

β-(o-Hydroxyphenylamino)vinyl Isobutyl Ketone (V). B. To 2.7 g of (I) were added 1.12 g of KOH in 30 ml of water and 2.9 g of isobutyl β-chlorovinyl ketone. This gave 0.6 g of light yellow crystals of (V), $C_{13}H_{17}NO_2$, R_f 0.45, mp 150-152°C (benzene), yield 13%.

The qualitative reaction for an OH group was positive.

From 2.18 g of o-aminophenol, 2.02 g of TEA in 50 ml of benzene, and 2.9 g of isobutyl β-chlorovinyl ketone was obtained 0.8 g (18%) of yellow crystals of (V). The compound was similar to the product obtained by method B.

N-Isovalerylbenzoxazolinone (VI). A. To 2.7 g of (I) were added 2.02 g of TEA in 50 ml of absolute benzene and 2.4 g of isovaleryl chloride. This gave 1.5 g of (VI), $C_{12}H_{13}NO_3$, R_f 0.86; mp 54-56°C (ethanol; yield 68%. Mass spectrum: m/z 219 (M^+), 204, 177, 162, 135.

Butyl β-(o-Hydroxyphenylamino)vinyl Ketone (VII). B. From 2.7 g of (I), 1.12 g of KOH in 30 ml of water, and 2.9 g of n-butyl β-chlorovinyl ketone was obtained 0.5 g (11%) of (VI), $C_{13}H_{17}NO_2$, R_f 0.45, mp 141-143°C (benzene). The qualitative reaction for an OH group was positive. Mass spectrum: m/z 219, 204, 177, 162, 135.

C. The benzoxazolinone salt was obtained from 2.7 g of (I) and 0.46 g of sodium in 30 ml of absolute ethanol; the ethanol was evaporated off and the residue was dissolved in dioxane, and to this solution 2.9 g of n-butyl β-chlorovinyl ketone was added with stirring. The mixture was stirred at room temperature for 2 h and was heated in a bath at 50-60°C for 2 h. This gave 0.56 g of (VII), identical with the product obtained by method B.

N-(β-Isovalerylvinyl)benzoxazolinethione (VIII). A. From 3.02 g of (II) and 2.02 g of TEA in 50 ml of absolute benzene and 2.9 g of isobutyl β-chlorovinyl ketone was obtained 1.6 g (30%) of (VIII), $C_{14}H_{15}NO_2S$, mp 108-110°C (petroleum ether); R_f 0.9. PMR spectrum (ppm): 1.1 (2 CH_3, 6 H, d, J = 7 Hz); 2.2 (CH_3–CH–CH_3, 1 H each, m); 2.35 (–CH_2–CH=, 2 H, m); 6.75 and 8.2 (CH=CH–, 1 H each, d, J = 10 Hz); 7.2-7.9 (Ar–H, 4 H, m). IR spectrum: 1670 cm^{-1}, $\nu_{C=O}$ (ketovinyl group). UV spectrum: λ_{max} 310 nm (log ε 5.01). Mass spectrum: m/z 261 (M^+), 218, 204, 177, 162, 151, 77. The qualitative reaction for a double bond was positive.

B. From 3.02 g of (II) and 1.12 g of KOH in 30 ml of water and 2.9 g of isobutyl β-chlorovinyl ketone was obtained 0.9 g (17%) of (VIII).

N-(β-Isovalerylvinyl)benzoxazolinone (IX). A. From 2.7 g of (I), 2.02 g of TEA, and 2.9 of isobutyl β-chlorovinyl ketone was obtained 1.5 g (30%) of (IX), $C_{14}H_{15}NO_3$, R_f 0.8, mp 91-93°C (ethanol). PMR spectrum (ppm): 0.9 (2 CH_3, 6 H, d, J = 7 Hz); 2.2 (CH_3–CH–CH_3, 1 H each, m); 2.35 (–CH_2–CH=, 2 H, m); 6.75 and 7.8 (CH=CH–, 1 H each, d, J = 15 Hz); 7.2 (Ar–H, 4 H, m).

N-(β-n-Butyrylvinyl)benzoxazolinethione (X). A. From 3.02 g of (II), 2.02 g of TEA, and 2.64 g of n-propyl β-chlorovinyl ketone was obtained 2.7 g (54%) of (X), $C_{13}H_{13}NO_2S$, R_f 0.9, mp 85-87°C (petroleum ether). UV spectrum: λ_{max} 310 nm (log ε 4.74). PMR spectrum (ppm): 0.95 (CH_3, 3 H, t); 1.5 (2 CH_2, 4 H, m); 2.47 (CH_2CO, 2 H, t); 6.6 and 8.2 (CH=CH—, 1 H each, d, J = 10 Hz); 7.01-7.7 (Ar—H, 4 H, m). IR spectrum: 1680 cm^{-1}, $\nu_{C=O}$ of a ketovinyl group; 935 cm^{-1}, deformation vibrations of a trans double bond.

B. From 3.02 g of (II) and 1.12 g of KOH in 30 ml of water and 2.64 g of propyl β-chlorovinyl ketonewas obtained 3.0 g (60%) of (X).

N-(β-n-Butyrylvinyl)benzoxazolinone (XI). A. From 2.7 g of (I) 2.02 g of TEA in 50 ml of benzene, and 2.64 g of propyl β-chlorovinyl ketone was obtained 1.15 g (22%) of (XI), $C_{13}H_{13}NO_3$, R_f 0.9, mp 95-97°C (ethanol). PMR spectrum (ppm): 0.9 (CH_3, 3 H, t); 1.6 (2 CH_2, 4 H, q); 2.5 (CH_2CO, 2 H, t); 6.7 and 7.8 (CH=CH—, 1 H each, d, J = 15 Hz); 7.0-7.4 (Ar—H, 4 H, m). IR spectrum: 1780 cm^{-1}, $\nu_{C=O}$ of an oxazolinone ring, 1700 cm^{-1} ($\nu_{C=O}$ of a ketovinyl group, 990 cm^{-1} deformation vibrations of a trans double bond. Mass spectrum: m/z 231 (M^+), 204, 188, 177, 162, 144, 135, 116.

N-(β-Propionylvinyl)benzoxazolinethione (XII). A. From 3.02 g of (II), 2.02 of TEA in 50 ml of benzene, and 2.36 g of ethyl β-chlorovinyl ketone was obtained 3.0 g (62%) of (XII), $C_{12}H_{11}NO_2S$, R_f 0.76, mp 98-100°C (petroleum ether). UV spectrum: λ_{max} 310 nm (log ε 4.29). PMR spectrum (ppm): 0.8 (CH_3, 3 H, t); 1.5 (2 CH_2, 4 H, m); 2.4 (CH_2CO, 2 H, t); 6.45 and 8.0 (CH=CH—, 1 H each, d); 6.9-7.6 (Ar—H, 4 H, m).

B. From 3.02 g of (II), 1.12 g of KOH in 30 ml of water and 2.36 g of ethyl β-chlorovinyl ketone was obtained 2.7 g (54%) of (XII).

N-(β-Propionylvinyl)benzoxazolinone (XIII). A. From 2.7 g of (I), 2.02 of TEA, and 2.36 g of ethyl β-chlorovinyl ketone was obtained 0.7 g (16%) of (XIII), $C_{12}H_{11}NO_3$, R_f 0.83, mp 132-134°C (ethanol). Mass spectrum: m/z 217 (M^+), 188, 144, 135, 116 .

B. From 2.7 g of (I), 0.46 g of metallic sodium in 30 ml of ethanol, and 2.36 of ethyl β-chlorovinyl ketone in 50 ml of acetonitrile was obtained 1 g (22%) of (XII).

N-(β-Acetylvinyl)benzoxazolinethione (XIV). A. From 3.02 g of (II), 2.02 g of TEA, and 2.09 g of methyl β-chlorovinyl ketone was obtained 2 g (45%) of (XIV), $C_{11}H_9NO_2S$, R_f 0.77, mp 136-138°C (petroleum ether). UV spectrum: λ_{max} 310 nm (log ε 4.45). IR spectrum: 1680 cm^{-1}, $\nu_{C=O}$ (ketovinyl group), 930 cm^{-1}, deformation vibrations of a trans double bond. Mass spectrum: m/z 219 (M^+), 177, 151, 122, 101.

B. From 3.02 g of (II), 1.12 g of KOH in 30 ml of water, and 2.09 g of methyl β-chlorovinyl ketone was obtained 1.1 g (25%) of (XIV).

β-(o-Hydroxyphenylamino)vinyl Methyl Ketone (XV). B. From 2.7 g of (I), 1.12 g of KOH in 30 ml of water, and 2.9 g of methyl β-chlorovinyl ketone was obtained 0.3 g (7%) of (XV), $C_{10}H_{11}NO_2S$, R_f 0.16, mp 156-158°C (ethanol). Mass spectrum: m/z 177 (M^+), 162, 144, 135, 120. The qualitative reaction for an OH group was positive.

N-(β-Chloroacetylvinyl)benzoxazolinethione (XVI). A. From 3.02 g of (II), 2.02 g of TEA in 50 ml of benzene, and 2.78 g of chloromethyl β-chlorovinyl ketone was obtained 2.1 g (41%) of (XVI), $C_{11}H_8NO_2SCl$, R_f 0.85, mp 101-103°C (petroleum ether). UV spectrum: λ_{max} 315 nm (log ε 5.16). PMR spectrum (ppm): 4.0 (CH_2Cl, 2 H, s); 6.9 and 8.4 (CH=CH, 1 H each, J = 9 Hz); 7.01-7.6 (Ar—H, 4 H, m). IR spectrum 1680 cm^{-1} (C=O of a ketovinyl group). Mass spectrum, m/z: 253 (M^+), 219, 204, 176, 162, 151, 134.

B. From 3.02 g of (II), 1.12 g of KOH in 30 ml of water, and 2.78 g (20 mmole) of chloromethyl β-chlorovinyl ketone was obtained 0.4 g (7%) of (XVI).

SUMMARY

1. It has been established that the reactions of benzoxazolinone and benzoxazolinethione with alkyl β-chlorovinyl ketones take place with the formation of N-(β-acylvinyl)benzoxazolinones and N-(β-acylvinyl)benzoxazolinethiones.

2. It has been shown that the reaction of benzoxazolinethione salts takes place at the hard atom of the ambident anion.

3. In the reactions of benzoxazolinone salts with alkyl β-chlorovinyl ketones the oxazoline ring opens and, with this, the configuration of the hydrogen atoms of the vinyl group changes.

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IMMOBILIZATION OF A PROTEASE ON GRAFTED POLYETHYLENES

T. I. Davidenko, A. V. Chuenko, and A. A. Bondarchuk

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It has been shown that when the protease of *Bacillus mesentericus* is immobilized on polyethylene with grafted-on polyacrylic acid by the carbodiimide method there is a considerable retention of its activity and an increase in its thermal stability, and the immobilized preparations are active on repeated use.

The wide use of proteases makes it necessary to obtain them in the immobilized state [1]. The immobilization of a protease from *Bacillus mesentericus* on Silochromes with the aid of various linking reagents distinguished by a considerable degree of binding of the protein has not given satisfactory results in relation to stability and repeated use [2]. It therefore appeared of interest to consider the possibility of immobilizing the protease on polyethylenes with grafted-on poly(acrylic acid) and poly(allyl alcohol). The advantage of polymeric supports of this type consist in the fact that the functional groups are readily modified; because of the "loose" packing of the grafted-on coating the functional groups are accessible for interaction with cross-linking reagents over the whole depth of the grafted-on layer, i.e., such polymeric supports combine within themselves the advantages of linear homopolymers and of three-dimensional polyligands.

The modification of the grafted polyethylenes was carried out by the following scheme using the carbodiimide, benzoquinone, and azide methods (see scheme, following page.)

As follows from Table 1, the maximum amount of protein is bound to polyethylene with grafted-on polyacrylic acid (PE-gr-PAAc) prepared by the carbodiimide method (ratios of enzyme to support 1:4 and 1:10). In this case, the ratio of linking agent to enzyme also has a considerable influence on the degree of binding of the protein. Thus, at a ratio of 1:2 20.6 mg of protein is bound per 1 g of support, and at a ratio of 1:20 only 1.5 mg. However, the caseinolytic activities of the immobilized preparations depend little on the ratios of linking agent to enzyme and of enzyme to support, amounting to 24.2-33.8%, which corresponds to the results of the immobilization of the *Bacillus mesentericus* protease on Silochromes modified with transition-metal salts [2]. With the azide method of linkage, both the degree of binding and the retention of the caseinolytic activity fall (to 5.5% and 12.2%, respectively). In the case of immobilization on polyethylene with grafted-on poly(allyl alcohol) (PE-gr-PAAl) with the aid of benzoquinone, however, inactive preparations were obtained.

When the protease immobilized on PE-gr-PAAc by the carbodiimide method was stored at 4°C for 4.5 months 94% of the initial activity was retained, while for the preparations immobilized on Silochromes only 22-68% of the activity was retained after a month.

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