# SYNTHESIS OF KETOVINYL DERIVATIVES OF 2-IMIDAZOLINONE

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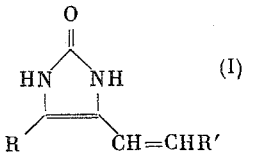
The ketovinyl and hydroxyvinyl derivatives of 2-imidazolinone of the (I) type are of interest as analogs of biotin and prostaglandins.

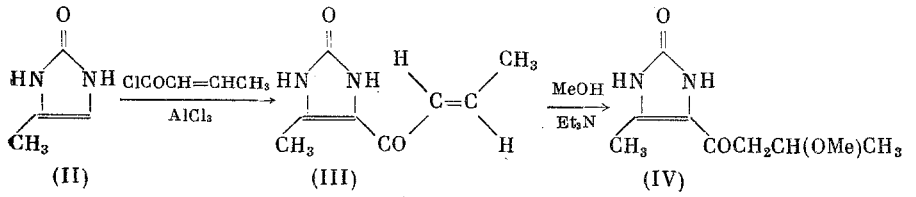


(I)

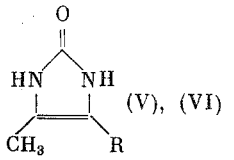
R = $CH_3$, R′ = $CO(CH_2)_2COOH$; R = $(CH_2)_6COOH$, R′ = $COC_5H_{11}$-$n$; R = $(CH_2)_6COOH$, R′ = $CHOHC_5H_{11}$-$n$.

In a search for ways of synthesizing (I) we studied in the present paper the insertion of ketovinyl and hydroxyalkylvinyl groups into 2-imidazolinone.

The reaction of 4(5)-methyl-2-imidazolinone (II) with crotonyl chloride in the presence of $AlCl_3$ gave 4-methyl-5-crotonyl-2-imidazolinone (III) in 43% yield, whose structure was proved by elemental analysis, the PMR spectrum, and the addition of MeOH in the presence of $Et_3N$ to give 4-methyl-5-(β-methoxybutyryl)-2-imidazolinone (IV):



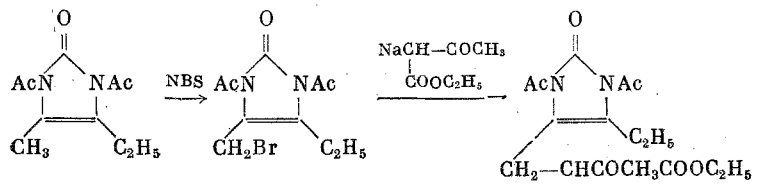
(II) (III) (IV)



(V), (VI)

R = $CHOHCH{=}CHCH_3$ (V); $CH{=}CHCHOHCH_3$ (VI).

In the next step of the synthesis it was proposed to reduce ketone (III) to alcohol (V), followed by the isomerization of alcohol (V) to alcohol (VI). However, a study of this path for inserting the hydroxyalkylvinyl group into the (II) molecule had to be stopped, since the reduction of (III) with $NaBH_4$ in alcohol was ill-defined and gave a complex mixture of products. The regioselective bromination of 1,3-diacetyl-4-methyl-5-ethyl-2-imidazolinone (VII) at the $CH_3$ group with N-bromosuccinimide in $CCl_4$ gave 1,3-diacetyl-4-bromomethyl-5-ethyl-2-imidazolinone (VIII), which when treated with sodioacetoacetic ester gave 1,3-diacetyl-4-ethyl-5-(2′-carbethoxy-3′-ketobutyl)-2-imidazolinone (IX):



(VII) (VIII) (IX)

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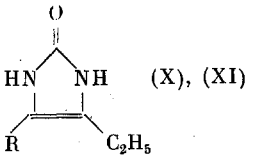
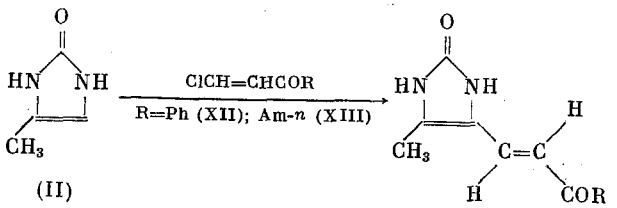


(X), (XI)

R=$CH_2CH_2COCH_3$ (X); $CH{=}CHCOCH_3$ (XI).

Further attempts to convert (IX) to ketones (X) and (XI) gave negative results: the hydrolytic cleavage of (IX) with either dilute HCl solution at 100°C or 5% KOH solution at 20° was accompanied by tarring and the formation of complex mixtures of products that could not be separated.

The path for inserting the ketovinyl moiety into (II) by the Friedel–Crafts reaction with chlorovinyl ketones [1] proved to be more promising:

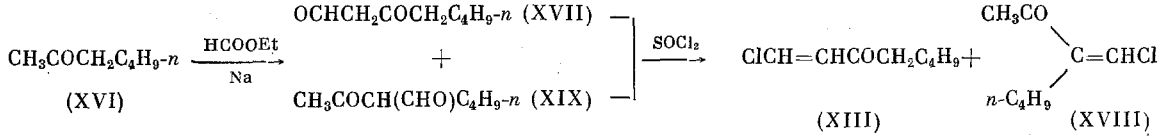


(II)

R=Ph (XIV); Am-*n* (XV).

The reaction of (II) with chlorovinyl phenyl ketone (XII) and chlorovinyl n-amyl ketone (XIII) respectively gave the 4-methyl-5-phenylketovinyl- and 4-methyl-5-n-amylketovinyl-2-imidazolinones (XIV) and (XV), whose structure and trans configuration was proved via the PMR spectra.

The starting chlorovinyl ketone (XIII) was synthesized by reacting methyl n-amyl ketone (XVI) with HCOOEt and Na in the presence of $Me_3SiCl$ in benzene and subsequent treatment of the intermediate formyl derivative (XVII) with $SOCl_2$:



(XVI) (XIII) (XVIII)

Based on the PMR spectral data, (XIII) is contaminated with 13% of the isomeric chlorovinyl ketone (XVIII), which was formed by the reaction of $SOCl_2$ with 3-formyl-2-heptanone (XIX), the formylation product of methyl n-amyl ketone (XVI) at the $CH_2$ group [2]. The formylation of (XVI) in the absence of $Me_3SiCl$ caused an increase in the amount of the isomeric formyl ketone (XIX) and a decrease in the yield of (XIII). The beneficial effect of $Me_3SiCl$ on the yields of (XVII) and (XIII) can be explained by the fact that the NaOEt, which facilitates the formylation of a methyl alkyl ketone at the $CH_2$ group [2], is removed from the reaction mixture:

$$Me_3SiCl + EtONa \rightarrow Me_3SiOEt$$

When (II) is reacted with excess chlorovinyl ketone (XIII), the contaminating isomeric chlorovinyl ketone (XVIII) did not affect the course of the process and did not lead to contamination of the desired product (XV).

## EXPERIMENTAL

The UV spectra were measured in alcohol solution on a Specord UV-VIS instrument, the IR spectra were taken as KBr pellets on a UR-20 spectrometer, and the PMR spectra were taken on a Tesla BS-497 instrument (100 MHz, internal standard = HMDS). The TLC was run on Silufol UV-254 (detection with $I_2$ vapors and in UV light).

4-Methyl-5-crotonyl-2-imidazolinone (III). With cooling (−10°C) (here and subsequently the bath temperature) and stirring, to a solution of 0.5 g of 4(5)-methyl-2-imidazolinone (II) [3] and 0.78 g of crotonyl chloride in 12 ml of nitrobenzene was added 2.33 g of $AlCl_3$ in 30 min, and the stirring was continued for another hour at 20° and for 13 h at 45°, after which the mixture was poured on ice, followed by the addition of $Na_2CO_3$ to pH 6-7 and 10 ml of ether. The precipitate was filtered, washed in succession with water, ether, and chilled acetone, and dried in air. We obtained 0.37 g (44%) of (III), decompn. above 250°, $R_f$ 0.54

(1:6 ethyl acetate (EA)—alcohol). Ultraviolet spectrum: 247 and 335 nm. Infrared spectrum ($\nu$, $cm^{-1}$): 1603, 1660, 1695. PMR spectrum ($CF_3COOH$, $\delta$, ppm): 1.64 d ($CH_3$), 2.17 s ($CH_3$), 6.27 d (trans-CH = $CHCH_3$, J = 15 Hz), 6.78 m (CH=$CHCH_3$), 9.70 m (NH). Found: C 55.90; H 6.10; N 15.80%. $C_8H_{10}N_2O_2 \cdot {}^1/_3H_2O$. Calculated: C 55.74; H 6.24; N 16.25%.

4-Methyl-5-(β-methoxybutyryl)-2-imidazolinone (IV). A mixture of 0.5 g of (III) and 4 drops of $Et_3N$ in 10 ml of MeOH was refluxed until all of the precipitate had dissolved, after which it was evaporated in vacuo, the residue was treated with acetone, and the precipitate was filtered and dried in air. We obtained 0.45 g (75%) of (IV), mp 176-177° (from alcohol), $R_f$ 0.55 (1.5-3.5 alcohol—EA). Infrared spectrum ($\nu$, $cm^{-1}$): 1603, 1640, 1722. PMR spectrum ($CF_3COOH$, $\delta$, ppm): 1.32 d ($CH_3CH$, J = 6 Hz), 2.48 s ($CH_3$), 3.02 m ($CH_2$), 3.44 s ($CH_3O$), 4.18 m (CH). Found: C 54.49; H 6.94; N 14.13%. $C_9H_{14}N_2O_3$. Calculated: C 54.53; H 7.12; N 14.14%.

1,3-Diacetyl-4-methyl-5-ethyl-2-imidazolinone (VII). A mixture of 4.5 g of 4-methyl-5-ethyl-2-imidazolinone [4] and 40 ml of $Ac_2O$ was heated for 4 h at 150-160° and then evaporated in vacuo. The residue was dissolved in the minimum amount of boiling alcohol, filtered, the mother liquor was kept for 2 h at 0°, and the precipitate was filtered, washed with chilled alcohol, and dried in air. We obtained 3.4 g (45%) of (VII), mp 68-69°, $R_f$ 0.79 (2.5:1.5 benzene—ether). Found: C 57.30; H 6.82; N 13.43%. $C_{10}H_{14}N_2O_3$. Calculated: C 57.14; H 6.67; N 13.33%.

1,3-Diacetyl-4-ethyl-5-(2'-carbethoxy-3'-ketobutyl)-2-imidazolinone (IX). A mixture of 1.3 g of (VII) and 1 g of N-bromosuccinimide in 15 ml of $CCl_4$ was refluxed for 1 h, after which the succinimide was filtered, the filtrate was evaporated, and to the residue [bromide (VIII), PMR spectrum ($CCl_4$, $\delta$, ppm): 1.14 g ($CH_3CH_2$, J = 7 Hz), 2.60 s ($2CH_3CO$), 2.78 q ($CH_3CH_2$), 4.68 s ($CH_2Br$)] was added a solution of sodioacetoacetic ester (from 0.16 g of Na and 3 ml of acetoacetic ester). The reaction mixture was stirred for 10 h at 20° and for 1 h at 70-80°, cooled to 20°, treated with water, and extracted with EA. The extract was dried over $MgSO_4$, evaporated, and the residue was chromatographed on $SiO_2$ (100/160 μm).

The impurities were eluted with benzene, while ketoester (IX) was eluted with a 9:1 benzene—ether mixture, mp 67-68° (after low-temperature crystallization from ether). The yield of (IX) was 0.2 g, $R_f$ 0.37 (3.5:1.5 ether—hexane). PMR spectrum ($CCl_4$, $\delta$, ppm): 0.92 m ($CH_3CH_2$), 1.07 m ($CH_3CH_2O$), 2.12 s ($CH_3CO$), 2.52 m ($CH_3CON$), 2.94 m ($CH_2$), 3.64 m (CH), 4.04 m ($CH_3CH_2O$). (The multiplet character of the signals in the PMR spectrum was probably caused by keto—enol tautomerism.) Found: C 56.96; H 6.80; N 8.10%. $C_{16}H_{22}N_2O_6$. Calculated: C 56.82; H 6.58; N 8.25%.

4-Methyl-5-phenylketovinyl-2-imidazolinone (XIV). With cooling (—10°) and stirring, to a solution of 0.4 g of (II) and 0.87 g of chlorovinyl phenyl ketone (XII) [5] in 18 ml of nitrobenzene was gradually added 1.63 g of $AlCl_3$, and the mixture was stirred for another 2 h at 20° and for 15 h at 45-50°. The reaction mixture was poured on ice, $Na_2CO_3$ was added to pH ∿6, and the precipitate was filtered, washed with ether, and extracted with hot acetone. After removal of the acetone we obtained 0.83 g (88%) of (XIV), mp 258-260° (decompn.) (from alcohol), $R_f$ 0.40 (EA). Ultraviolet spectrum: 264 and 390 nm. PMR spectrum ($CF_3COOH$, $\delta$, ppm): 2.36 s ($CH_3$), 7.16 d (trans-CH=CHCO, J = 16 Hz), 7.56 m (CH=CHCO, m- and p-protons of $C_6H_5$), 7.89 m (o-protons of $C_6H_5$). Found: C 68.30; H 5.57; N 12.09%. $C_{13}H_{12}N_2O_2$. Calculated: C 68.41; H 5.30; N 12.27%.

1-Chlorovinyl n-amyl ketone (XIII). With stirring, to a solution of 3.3 ml of methyl n-amyl ketone (XVI), 4 ml of HCOOEt, and 0.5 ml of $Me_3SiCl$ in 40 ml of benzene was added 1 g of Na (as thin sheets) in 30 min, after which the mixture was stirred for another 3 h at 20°, kept for ∿12 h at 20°, treated with water and ice, and, with ice cooling, the alkaline layer was acidified with dilute HCl solution and extracted with benzene. The extract was dried over $MgSO_4$ and evaporated in vacuo. The residual formyl derivatives (XVII) and (XIX) were dissolved in 20 ml of benzene, 3 ml of $SOCl_2$ was added, the mixture was kept for 5 h at 20°, evaporated, and the residue was vacuum-distilled. We obtained 1.7 g (40%) of a mixture of (XIII) [6] and 1-chloro-2-n-butyl-1-butene-3-one (XVIII), $n_D^{20}$ 1.4633, $R_f$ 0.63 (benzene). The PMR spectrum of this mixture ($CCl_4$) has the signals of the $CH_2CO$ (t, 2.33 ppm) and $CH_3$ (s, 2.13 ppm) groups, with a 5:1 ratio of the integral intensities, which corresponded to 13% of (XVIII) as impurity.

The formylation of methyl n-amyl ketone (XVI) in the absence of $Me_3SiCl$, followed by treatment of the mixture of formyl derivatives (XVII) and (XIX) with $SOCl_2$, gave in 35% yield a mixture of chlorovinyl ketones (XIII) and (XVIII) in a 1.5:1 ratio.

4-Methyl-5-n-amylketovinyl-2-imidazolinone (XV). With cooling (−10°) and stirring, to a solution of 0.4 g of (II) and 1.5 g of a mixture of chlorovinyl ketones (XIII) and (XVIII) in 10 ml of nitrobenzene was gradually added 1.63 g of $AlCl_3$, after which the mixture was stirred for another hour at 20° and for 16 h at 42-46°. After the above described workup we obtained 0.77 g (89%) of (XV), mp 190-192° (decompn.) (from 10:1 EA—alcohol), $R_f$ 0.60 (0.5:4.5 alcohol—EA). Ultraviolet spectrum: 357 nm. PMR spectrum ($CF_3COOH$, δ, ppm): 0.80 t ($CH_3CH_2$, J = 5 Hz), 1.37 m, ($CH_2CH_2CH_2$), 2.32 s ($CH_3$), 2.72 t ($CH_2CO$, J = 8 Hz), 6.40 d (trans-CH=CHCO, J = 16 Hz), 7.10 d (trans-CH=CHCO, J = 16 Hz). Found: C 60.18; H 8.72; N 11.47%. $C_{12}H_{18}N_2O_2 \cdot H_2O$. Calculated: C 59.98; H 8.39; N 11.65%.

## CONCLUSIONS

1. The reaction of 4(5)-methyl-2-imidazolinone with crotonyl chloride, chlorovinyl phenyl ketone or chlorovinyl n-amyl ketone in the presence of $AlCl_3$, respectively, gives 4-methyl-5-crotonyl-, 4-methyl-5-phenylketovinyl- or 4-methyl-5-n-amylketovinyl-2-imidazolinone.

2. The regioselective bromination of 1,3-diacetyl-4-methyl-5-ethyl-2-imidazolinone with N-bromosuccinimide leads to 1,3-diacetyl-4-bromomethyl-5-ethyl-2-imidazolinone, which with sodioacetoacetic ester gives 1,3-diacetyl-4-ethyl-5-(2'-carbethoxy-3'-ketobutyl)-2-imidazolinone.

3. The reaction of methyl n-amyl ketone with ethyl formate and sodium in the presence of $Me_3SiCl$ and subsequent treatment of the formylation products with $SOCl_2$ gives a mixture of chlorovinyl n-amyl ketone and 1-chloro-2-n-butyl-1-buten-3-one in a 7.5:1 ratio.

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# ACYLATION OF 4,6-DIAMINO-2-MERCAPTOPYRIMIDINE AND ITS SALTS WITH CARBOXYLIC ACID CHLORIDES


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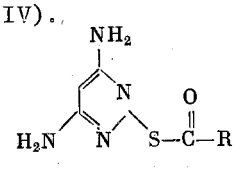
The data on the acylation of aminomercaptopyrimidines are contradictory [1-7]. We studied the acylation of 4,6-diamino-2-mercaptopyrimidine (I) and its salts with carboxylic acid chlorides (CAC) under various conditions. The formation of three types of monoacylated derivatives of (I) is theoretically possible: 2-acylthio-4,6-diaminopyrimidines (II), 1-acyl-4,6-diamino-1,2-dihydro-2-pyrimidinethiones (III), and 6-amino-4-acylamido-1H(3H)-dihydro-2-pyrimidinethiones (IV).



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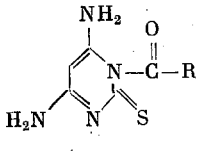

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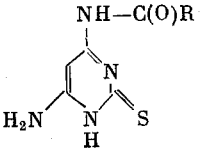

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