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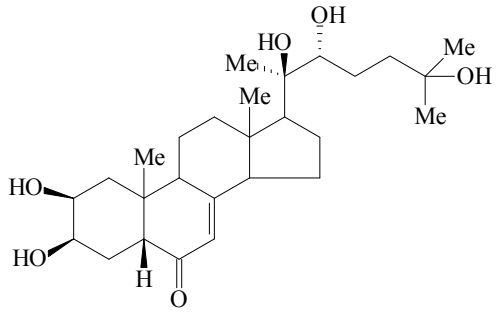
SYNTHESIS OF SOME ISOXAZOLINE, ISOXAZOLE AND PYRAZOLE CARBOXYLIC ACIDS AS THE PRECURSORS OF NEW 1,2-DIACYL-1-ALKYLHYDRAZINES

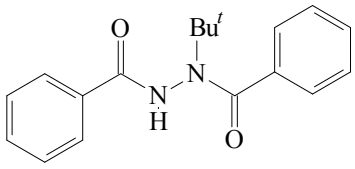
A number of isoxazoline, isoxazole and pyrazole carboxylic acids or their esters has been synthesized via the 1,3-dipolar cycloaddition of corresponding nitrile oxides or diazomethane to unsaturated dipolarophiles. The obtained substances are of the interest as the precursors of new 1,2-diacyl-1-alkylhydrazines which are perspective as highly selective insecticides.

Introduction. The processes of insect moulting and metamorphosis are known to be controlled by several hormones, particularly by ecdysteroids, which major representative being 20-hydroxyecdyzone [1, 2]:



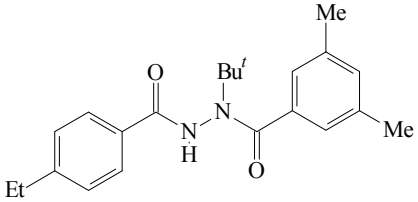
The disorders of normal moulting and metamorphosis processes under the influence of exogenous ecdysteroids or compounds imitating their biological action usually lead to insects death. Such compounds therefore refer to insect growth regulators and are of interest as perspective insecticides [3].

At the 1980-s end the hydrazine acyl derivatives **1** have been found to possess such hormonal activity [4, 5]. The compound RH 5849 is the first representative of ecdysteroids agonists of 1,2-diacyl-1-alkyl hydrazine series [4, 5], which however haven't found practical employment due to the low bioactivity.

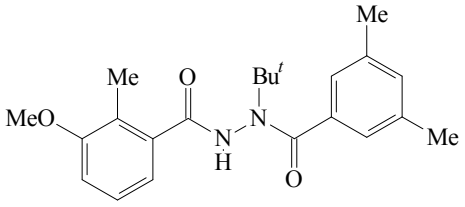


RH 5849

The first commercial product of this series is tebufenozide RH 5992 [6, 7] thereafter – metoxyfenozide RH 2485 [7, 8]:

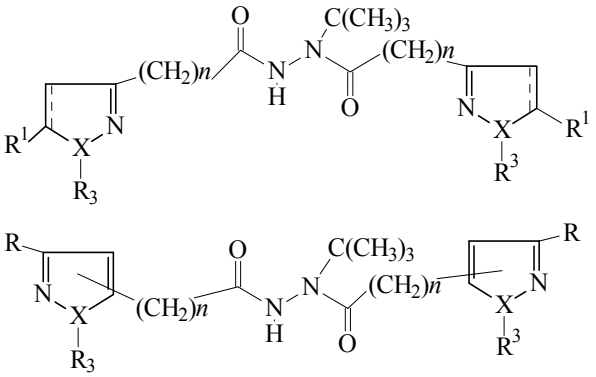


Tebufenozide RH 5992



Metoxyfenozide RH 2485

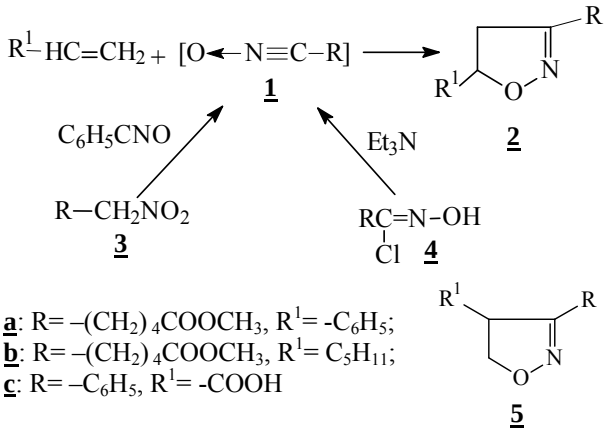
Synthesis of such compounds includes the interaction between *tert*-butylhydrazine hydrochloride and acid chlorides of the corresponding aromatic acids [9, 10]. Therefore 1,2-diacyl-1-alkyhydrazines containing 2-isoxasoline, isoxazole or pyrazole cycles have been suggested to be perspective as highly selective insecticides:



The objective of this research is to accomplish the synthesis of a number of isoxazoline, isoxazole and pyrazole carboxylic acids derivatives as the precursors of new 1,2-diacyl-1-alkylhydrazines.

Main part. A number of 2-isoxazolines containing carboxyl group in their substituent have been synthesized in order to obtain some corresponding heterocyclic carboxylic acids or their esters (Scheme 1). The 1,3-dipolar cycloaddition reaction of styrene and nitrile oxide **1** led to 3-(4-metoxycarbonylbutyl)-5-phenyl isoxazoline **2a** as an oil (86.6% yield), the nitrile oxide being generated from methyl 6-nitrohexanoate **3** by the action of phenyl isocyanate (Scheme 1) (Table).

The isolation of product **2a** has being carried out by column chromatography on silica gel, the eluent being ether – light petroleum.



Scheme 1

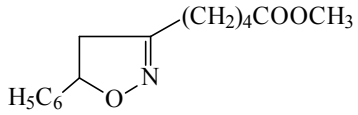
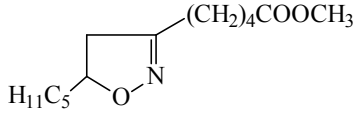
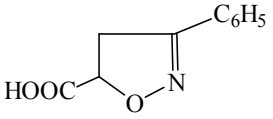
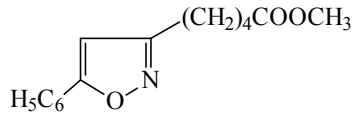
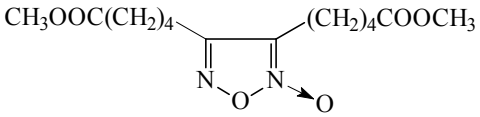
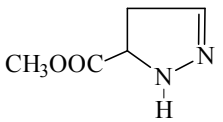
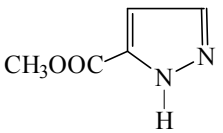
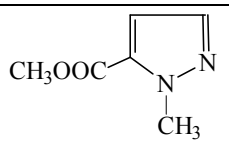
Similarly, the interaction of methyl 6-nitrohexanoate **3** with heptene-1 gave 3-(4-metoxycarbonylbutyl)-5-pentyl isoxazoline **2b** as an oil (88.8% yield) (Scheme 1) (Table).

In both cases the reaction proceeded with high regioselectivity, as the presence of regioisomer **5** wasn't detected in the reaction mixture. It should be mentioned that methyl ester of 6-nitrohexanoic acid has been used as a nitrile oxide precursor in both these syntheses. These ester was synthesized in three stages from cyclohexanone in preparative quantities.

The products structure has been confirmed by modern spectral methods. The absorption band of the ester group at 1736 sm^{-1} is the most characteristic in the infra-red spectrum of isoxazoline **2a**.

The ^1H NMR spectrum of the product **2a** (Fig. 1) contains the proton signals of isoxazoline heterocycle, particularly H-5 signal is observed as doublet of doublets at 5.53 ppm while each of two H-4 – as doublet of doublets at 3.35 and 2.89 ppm regions respectively due to a spin-spin coupling (SSC) with H-5 and with the second H-4.

Yields and physical properties of isoxazoline, isoxazole and pyrazole carboxylic acids and their derivatives

Compound number	Structural formula	Molecular weight, M	Empirical formula	Yield, %	Mp, °C
2a		261.32	$C_{15}H_{19}NO_3$	86.6	Oil
2b		255.,35	$C_{14}H_{25}NO_3$	88.8	Oil
2c		191.18	$C_{10}H_9NO_3$	45.9	140–142
6a		259.30	$C_{15}H_{17}NO_3$	59.6	63–66
7a		314.33	$C_{14}H_{22}N_2O_6$	19.4	Oil
9		128.13	$C_5H_8N_2O_2$	100	66–68
10		126.11	$C_5H_6N_2O_2$	19.4	134–136
11		140.14	$C_6H_8N_2O_2$	55.5	Oil

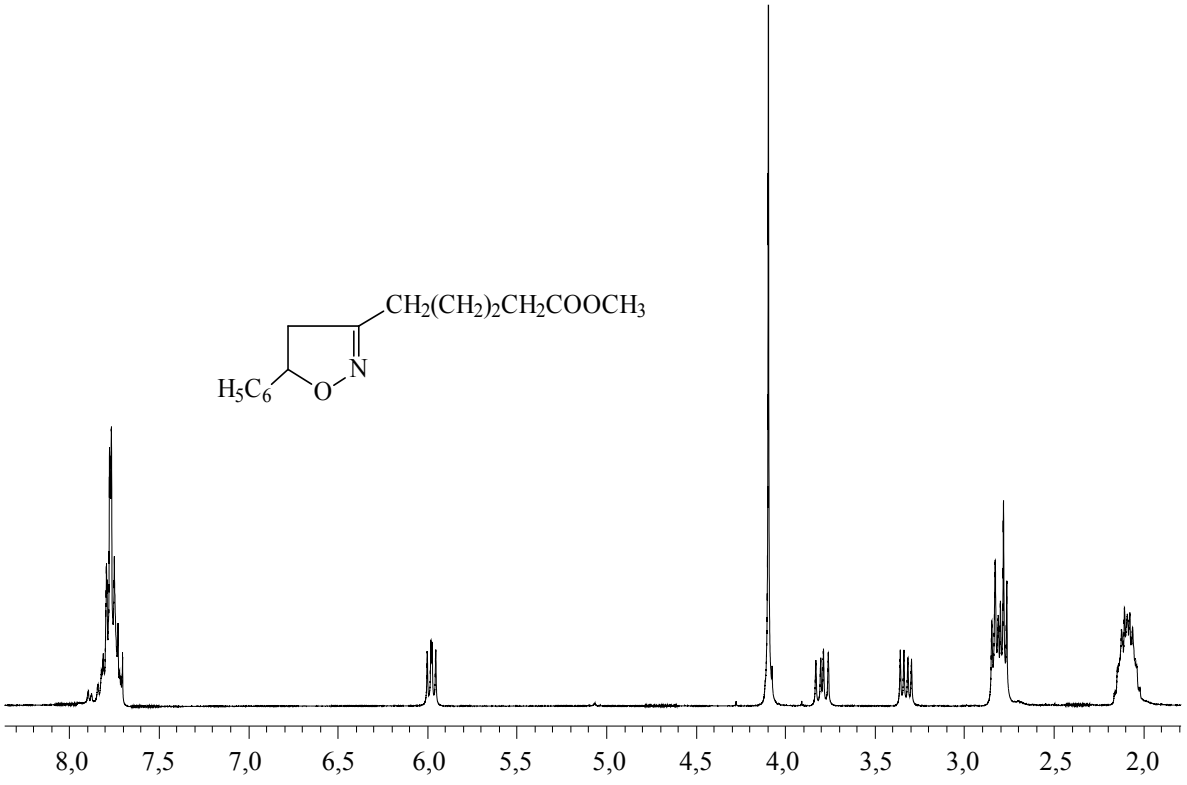


Fig. 1. ^{1}H NMR spectrum of 3-(4-metoxycarbonylbutyl)-5-phenylisoxazoline **2a**

Aromatic protons signals of the benzene ring (7.29–7.37 m) as well as the singlet signal of the ester methyl group (3.66 ppm) and methylene protons signals of carboxyalkyl substituent are also observed in this spectrum.

Signals of all carbon atoms present in the suggested structure are observed in the ^{13}C NMR spectrum of isoxazoline **2a**. The most characteristic signals are those of the following C-atoms: ester group (173.18 ppm), C-3 isoxazoline heterocycle (157.60 ppm, C=N), and benzene ring (140.92 + + 128.18+127.50+127.27) ppm, C_{ar}).

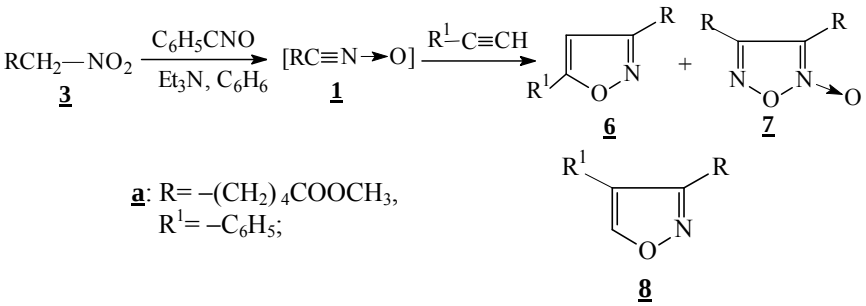
Another method of the generation of nitrile oxide **1** was realized in the 3-phenylisoxazoline-5-carboxylic acid **2c** synthesis (Scheme 1). Thus, benzaldehyde oxime has been prepared previously. Subsequently it was chlorinated by N-chlorosuccinimide with the formation of the corresponding hydroximoyl chloride **4**. The latter was converted by the action of triethylamine to nitrile oxide **1** which was trapped by acrylic acid successively. The reaction led to 3-phenylisoxazoline-5-carboxylic acid **2c**, the yield being 46% (Scheme 1) (Table).

It should be mentioned that regioisomeric 3-phenylisoxazoline-4-carboxylic acid **5c**, was formed alongside with the main product, the proton signals of this byproduct as an impurity were observed in the ^{1}H NMR spectrum of the raw material obtained after the initial water treatment of the reaction mixture.

The introduction of isoxazole cycle fragment into the structure of ecdysteroids agonists of 1,2-diacyl-1-alkylhydrazine series seems to be perspective as that of isoxazoline heterocycle. Therefore, synthesis of the corresponding isoxazoles with a carboxylic group in the substituent has been carried out. For this purpose, the interaction between phenylacetylene and nitrile oxide has been carried out, the nitrile oxide being produced from methyl 6-nitrohexanoate by phenyl isocyanate action (Scheme 2).

Thus, nitro compound **3a** by phenyl isocyanate was converted to nitrile oxide **1** which participated in the 1,3-dipolar cycloaddition reaction with phenyl acetylene. The reaction gave 3-(4-metoxycarbonylbutyl)-5-phenyisoxazole **6a** in high yield (Table). It should be noted that furoxane **7a** (19.4% yield) has been isolated by means of chromatography in addition to the main product. Since furoxane **7a** contains two metoxycarbonylbutyl substituents it also presents interest as an intermediate in the synthesis of biologically active hydrazine acyl derivatives. The reaction proceeded with high regioselectivity, i.e. the formation of isomer **8a** didn't occur.

The products structure has been proved by modern spectral methods. The most characteristic signal in the isoxazole **6a** ^{1}H NMR spectrum is the isoxazole proton singlet at 6.37 ppm (Fig. 2). There are also aromatic proton signals of the benzene ring at 7.74 and 7.42 ppm regions as well as the ester methyl group singlet signal (3.66 ppm) and signals of substituent methylene protons in the spectrum.



Scheme 2

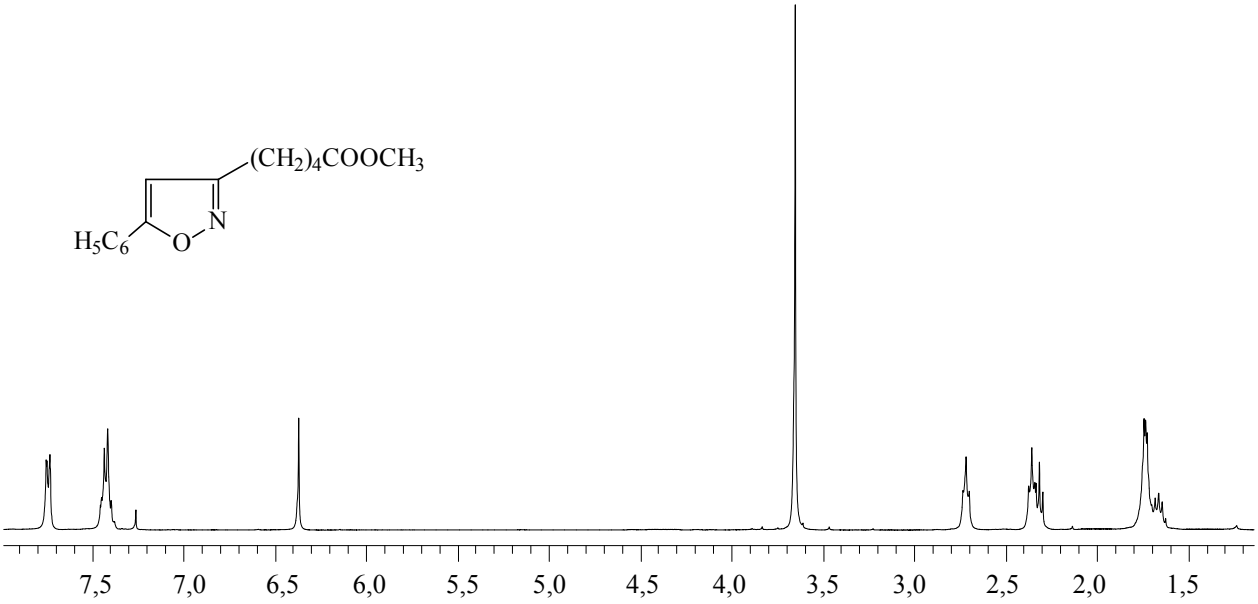
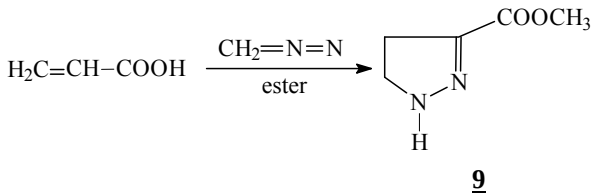


Fig. 2. ^{1}H NMR spectrum of 3-(4-metoxycarbonylbutyl)-5-phenylisoxazole

The signals of all carbon atoms present in the suggested structure are observed in the ^{13}C NMR spectrum of isoxazole **6a**. The most characteristic are ester carbonyl group signal (173.70 ppm) as well as those of isoxazole heterocycle: 169.56 ppm (C-5); 164.03 ppm, (C=N); 99.00 ppm (C-4) and of benzene ring: 129.91 + 128.83 + 127.60 + 125.66 ppm (C_{ar}).

The next stage of this research included the interaction of diazomethane and acrylic acid in order to synthesize the carboxylic acids with pyrazole heterocycle fragment (Scheme 3). The cycloaddition reaction proceeded with high regioselectivity and led to 4,5-dihydro-1H-pyrazole-3-carboxylate **9** with a quantitative yield.



Scheme 3

Alongside with the cycloaddition reaction carboxylic group methylation took place with the formation of the corresponding ester.

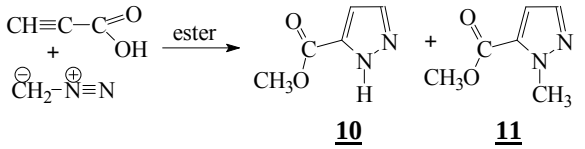
The structure of the compound **9** has been proved by spectral characteristics of IR, ^{1}H NMR and ^{13}C NMR spectra. The absorption band of the ester group conjugated with π-electrons of the C=N bond is observed at 1698 cm^{-1} in the pyrazoline **9** IR spectrum. There is also the absorption band of N-H bond at 3312 cm^{-1} region as well as those of the methyl ester group at 1441 and 1350 cm^{-1}.

Pyrazoline cycle proton signals appear in the ^{1}H NMR spectrum of this compound. The signal of the two chemically equivalent protons H-5 is observed as a triplet at 3.62 ppm region and has a spin-spin coupling constant with H-4 J = 10.8 Hz. H-4 signal is seen in a higher field area as a triplet (2.88 ppm) with the same SSCC. Methyl ester group protons signal is observed as a singlet at 3.80 ppm.

The 1,3-dipolar cycloaddition reaction of acetylene carboxylic acid and diazomethane has been carried out to synthesize the carboxylic acids with pyrazole heterocycle (Scheme 4) (Table).

The diazomethane solution in diethyl ether has been added to unsaturated acid solution during two hours with cooling (0°C) and stirring. The two main reaction products have been isolated by

means of column chromatography: methyl 1H-pyrazole-5-carboxylate **10**, the yield being 19.4% (Mp = 134-136°C); and methyl N-methylpyrazole-5-carboxylate **11** (oil), the yield being 55.5%. On the basis of the obtained products composition data, the methylation of the carboxylic group and partially of the pyrazole cycle nitrogen atom is obviously to proceed by diazomethane action along with the cycloaddition reaction.



Scheme 4

High reaction regioselectivity is probably due to the possibility of intramolecular hydrogen bond formation in isomer **10**, while this ability is absent for the isomers with metoxycarbonyl group in the 3-d and 4-th position of heterocycle.

The structure of the obtained compound has been proved by spectral characteristics of IR, ^{1}H NMR and ^{13}C NMR spectra. The absorption band of the N-H bond at 3128 cm^{-1} region as well as the characteristic absorption band of the ester group (1734 cm^{-1}) is observed in the IR spectrum of compound **10**. The most characteristic signals in the ^{1}H NMR spectrum of compound **10** are those of pyrazole cycle protons. Signal H-3 appears at 7.86 ppm as a doublet and has a spin-spin coupling constant equal to 2.3 Hz (with H-4). Signal H-4 is observed in a higher field area as a doublet (6.85 ppm, J = 2.3). Methyl ester group protons appear as a singlet at the 3.96 ppm region. Signals of all carbon atoms present in the proposed structure are observed in the pyrazole **10** ^{13}C NMR spectrum: of ester group (162.87 ppm), of pyrazole heterocycle: 142.31 ppm (C-5); 131.21 ppm (C=N); 107.50 ppm (C-4) and 51.82 ppm (CH_3).

The ^{1}H NMR spectrum of compound **11** contains similar protons signals as the compound **10** while the additional N-methyl group singlet signal is observed at 4.16 ppm region.

Experimental Section. ^{1}H and ^{13}C NMR spectra of substances solutions in $CDCl_3$ containing HMDS as an internal standard have been recorded with Bruker AVANCE spectrometer (400 MHz). The reaction courses was monitored by thin-layer chromatography (TLC) on silica gel plates Kieselgel 60 F_{254} (Merck), the eluent being ether – light petroleum, developer: iodine or 4% $KMnO_4$ solution. The used solvents were purified according to standard procedures [11].

Procedure of 1,3-dipolar cycloaddition reaction using nitro compounds (method A). 0.967 g (0.0082 mol, 0.88 ml) of phenyl isocyanate and then few drops of triethylamine were added to a stirred solution of 0.6860 g (0.0039 mol) of methyl 6-nitrohexanoate and 0.4166 g (0.0040 mol) of styrene in absolute benzene (4ml). The reaction mixture has been stirred for 18 hours at room temperature, then few drops of water were added. The diphenyl urea residue was filtered out. After solvent evaporation under reduced pressure the obtained residue was separated by the column chromatography on silica gel with ether – light petroleum using gradient increase of eluent polarity. These gave 0.8815 g (86.6% yield) **of 3-(4-metoxycarbonylbutil)-5-phenyl isoxazoline 2a** as an oil.

IR spectrum (film), sm^{-1}: 3031, 2949, 1736, 1590, 1493.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1,60–1,70 m (4H, $(CH_2)_2$), 2.33 m (2H, $(C\underline{H}_2CO_2CH_3)$, 2.39 m (2H, $(C(=N)CH_2)$, 2.89 dd (1H, H^B-4, J^{gem} = 17.1; J_2 = 8.2 Hz), 3.35 dd (1H, H^A-4, J^{gem} = 17.1; J_2 = 11.0 Hz), 3.66 s (3H, CO_2CH_3), 5.53 dd (1H, H-5; J_1 = 10.8; J_2 = 8.2); 7.29–7.37 m (5H; H_{ar}).

^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 173.18 (COOR), 157.60 (C=N); 140.92 ($C^5{}_{ar}$) 128.18 + 127.50 + 125.27 (C_{ar}), 80.78 (C-5), 51.00 ($CO_2\underline{C}H_3$), 44.77 (C-4), 33.02 ($\underline{C}H_2CO_2R$); 26,88 (C(=N)$\underline{C}H_2$), 25.20 ($CH_2CH_2CO_2R$); 23.90 (C(= N) $CH_2\underline{C}H_2$).

3-(4-metoxycarbonylbutyl)-5-phenyl isoxazoline 2b has been obtained using the same procedure as an oil, the yield being 88.8%.

IR spectrum (film), sm^{-1}: 2954, 2932, 2860, 1738, 1622, 1551, 1435.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 0.83 t (3H, CH_3); 1,25 m (4H, $(C\underline{H}_2)_2CH_3$); 1.28–1.56 m (4H, $(CH_2)_2$); 1.56–1,66 m (4H, $(C\underline{H}_2)_2CH_2CO_2CH_3$), 2.30 m (4H, $C(=N)C\underline{H}_2$ + $C\underline{H}_2CO_2CH_3$ CH_2) 2.48 dd (1H, H^B-4, J^{gem} = 16.9; J_2 = 8.0 Hz), 2.91 dd (1H, H^A-4, J^{gem} = 16.6; J_2 = 10.0 Hz), 3.62 s (3H, CO_2CH_3); 4.46 m (1H, H-5; J_1 = 10.0; J_2 = 8.2); 7.29–7.37 m (5H; H_{ar}).

^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 173.57 (COOR), 158.18 (C=N); 80,01 (C-5), 51.32 ($CO_2\underline{C}H_3$), 40.50 (C-4), 35.02 ($\underline{C}H_2C^5$-O); 33.36 ($\underline{C}H_2CO_2R$), 31.45 ($\underline{C}H_2CH_2CH_3$); 27.37 (C(= N) $\underline{C}H_2$), 25.56 ($\underline{C}H_2CH_2CO_2R$), 25.07 ($\underline{C}H_2(CH_2)_2CH_3$); 24,21 ($C(=N)CH_2\underline{C}H_2$), 22.35 ($\underline{C}H_2CH_3$) 13.78 ($CH_3$).

Methyl 5-(5-phenyl isoxazole-3-yl)pentanoate has been obtained as crystals using method A, the yield being 59.6%. M.p. 63–66 °C.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 7.74 d (2H, H_{ar}) 7.42 m (3H; H_{ar}), 6.37 s (1H, H_{isox}-4), 3.66 (3H, CO_2CH_3), 2.72 t (2H, J = 6.4, $C(=N)CH_2$) 2.36 t (2H, J = 6.7; $C\underline{H}_2CO_2CH_3$); 1.70–1.77 m (4H, $(C\underline{H}_2)_2CH_2CO_2CH_3$).

^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 173.70 (COOR), 169.56 (C-5), 164.03 (C=N); 129.91 (C_{ar}-1'), 128.83 (C_{ar}-3'+ C_{ar}-5'), 127.52 (C_{ar}-4'), 125.66 (C_{ar}-2' + C_{ar}-6'), 99.00 (C_{isox}-4) 51.43

($CO_2\underline{C}H_3$), 33.50 ($\underline{C}H_2CO_2R$); 27,60 (C(=N)$\underline{C}H_2$); 25.73 (C(= N)$CH_2\underline{C}H_2$), 24.33 ($\underline{C}H_2CH_2CO_2R$).

Furoxane 7 has been obtained as an oil.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.66 s (3H, CO_2CH_3), 2.59 t (2H, *J* = 6.9, C(=N)CH_2); 2.39 t (2H, *J* = 6.9; $C\underline{H}_2CO_2CH_3$); 1.73–1.82 m (4H, $(C\underline{H}_2)_2CH_2CO_2CH_3$).

^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 173.64 (COOR), 151.66 (C=N); 145.51 (C=N); 51.53 ($CO_2\underline{C}H_3$) 33.53 ($\underline{C}H_2CO_2R$); 34.26 (C(=N)$\underline{C}H_2$); 26.04 (C(=N)$CH_2\underline{C}H_2$), 24.04 ($\underline{C}H_2CH_2CO_2R$).

Procedure of 1,3-dipolar cycloaddition reaction using hydroxymoilchloride (method B). At room temperature 3.2797 g (0.025 mol) of N-chlorosuccinimide was added in small portions to a stirred solution of 2.9734 g (0.024 mol) of oxime benzaldehyde in dichloromethane (25 ml). The reaction course was monitored by TLC. After the disappearance of oxime the reaction mixture was poured into 10 ml of water. The water layer was extracted with dichloromethane. The combined organic extracts were dried on anhydrous sodium sulphate. The solvent was removed in a rotary evaporator. The obtained hydroximoyl chloride **4** was further used in the 1,3-dipolar cycloaddition reaction according to the following procedure.

At room temperature a solution of hydroximoyl chloride in 20 ml dichloromethane and a solution of 2.4286 g (0.024 mol) triethylamine in 10 ml dichloromethane were added dropwise from two dropping funnels simultaneously to a stirred solution of 1.8015 g (0.025 mol) freshly distilled acrylic acid in 10 ml dichloromethane. Stirring was continued at room temperature. The reaction course was monitored by TLC. Then the reaction mixture was filtered from triethyl ammonium chloride, the filtrate was washed with water and the organic layer was dried on anhydrous sodium sulphate. After removing of drying agent the solvent was evaporated under reduced pressure. The obtained residue was purified by column chromatography on silica gel with the gradient increase of the eluent polarity (ether – hexane, ethanol – ether).

The yield of **3-phenyl-isoxazoline-5-carboxylic acid 2a** was 45.9%. M.p. 140–142 °C.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3,56–3.64 m (2H; J_1 = 10.4; CH_2-4), 5.13 dd (1H; J_1 = 10.4; J_2 = 8.6; H-5), 7.34 m (3H; H_{ar}), 7.60 m (2H, H_{ar}).

^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 173.3 (COOR), 156.5 (C=N); 130.8 (C_{ar}-1) 128.9 + 128.1 + 127.0 (C_{ar}), 80.8 (C-5), 39.3 (C-4).

Impurity of regioisomer - **3-phenyl-isoxazoline-4-carboxylic acid** - was observed in the ^{1}H NMR spectrum recorded for crude product after initial water treatement of the reaction mixture.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 5.81 dd (1H, J_1 = 10.4; J_2 = 1.5; H-4), 6.09 dd (1H, J^{gem} = 17.3; J_2 = 10.4, H^B-5), 6.38 dd (1H, J^{gem} = 17.3; J_2 = 1.5; H^A-5), 7.34 m (3H; H_{ar}) 7.60 m (2H; H_{ar}).

Methyl 4,5-dihydro-1H-pyrazole-3-carboxylate. The 90 ml dilute ether solution of diazomethane containing 0.0150 mol of reagent was added at 0 °C to a stirred solution of 0.5255 g (0.0073 mol, 0.5 ml) acrylic acid in 50 ml absolute diethyl ether (up to persistent yellow color of the reaction mixture). Stirring was continued for 1 hour at low temperature, whereupon it was left overnight at room temperature. Then the solvent was evaporated under reduced pressure, and 3-metoxy carbonyl pyrazoline was obtained as crystals, the yield being 0.926 g (0.0073 mole, 100%). M.p. 66–68 °C.

IR spectrum (KBr), sm^{-1}: 3312, 2988, 2950, 2883.1697, 1544, 1441, 1350, 1314, 1262, 1214, 1107.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 5.80 br. s (1H, NH); 3.80 s (3H, OCH_3), 3.62 m (2H, H-5, *J* = 10.8 Hz), 2.88 m (2H, H-4, *J* = 10.8).

^{13}C NMR spectrum ($CDCl_3$), δ, ppm 172.04 (CO_2R); 145.63 (C=N); 52.01 (C-5); 51.91 ($CO_2\underline{C}H_3$); 30.45 (C-4).

Reaction of diazomethane and acetylene carboxylic acid. The 150 ml dilute ether solution of diazomethane was added at 0 °C to a stirred solution of 1.0110 g (0.0144 mol) acetylene carboxylic acid in 50 ml absolute diethyl ether (up to persistent yellow color of the reaction mixture).

Stirring was continued for 1 hour at low temperature and then for 12 hours at room temperature. After that the solvent was removed under reduced pressure, the obtained residue separation by column chromatography gave methyl 1H-pyrazole-5-carboxylate **11** (M.p.134–136° C) (0.352 g, 19.4% yield) and methyl N-methylpyrazole-5-carboxylate **12** (oil) (1.119 g, 55.5% yield).

Methyl 1H-pyrazole-5-carboxylate (19.4%). Crystals. M.p. 134–136 °C.

IR spectrum (KBr), sm^{-1}: 3128, 3042, 2904, 2833, 1734, 1540, 1466, 1370, 1308, 1198, 1168, 1059, 1000.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.88 d (1H, H-3, *J* = 2.3 Hz), 6.85 d (1H, H-4, *J* = 2.3 Hz), 3.95 (3H,-OCH_3).

^{13}C NMR ($CDCl_3$), δ, ppm 162.87 (CO_2R); 142,31 (C=N); 131.21 (C-3); 107.50 (C-4), 51.82 ($CO_2\underline{C}H_3$).

Methyl N-methylpyrazole-5-carboxylate (55.5%). Oil.

IR spectrum (KBr), sm^{-1}: 2954, 2915, 2841.1726, 1515, 1460, 1320, 1255, 1193, 1123, 1019.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.43 d (1H, H-5, *J* = 2.05 Hz), 6.81 d (1H, H-4, *J* = 1.79 Hz), 4.18 s (3H,-NCH_3), 3.88 s (3H,-OCH_3).

^{13}C NMR spectrum ($CDCl_3$), δ, ppm 160.27 (CO_2R); 142.30 (C=N); 137.73 (C-5); 111.20 (C-4), 51.83 ($CO_2\underline{C}H_3$); 39.45 (N-CH_3).

Conclusion. The scheme of isoxazoline, isoxazole and pyrazole carboxylic acids derivatives pre-

paration via 1,3-dipolar cycloaddition reaction has been realized.

The synthesis of these heterocyclic acids and their esters has been shown to proceed with high regioselectivity.

The cycloaddition reaction along with the methylation of the carboxylic group and partially of the pyrazole cycle nitrogen atom is obviously to occur as a result of interaction between diazomethane and acetylene carboxylic acid.

The synthesized compounds are the precursors for synthesis of new 1,2-diacylhydrazines which are perspective as insecticides.

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