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REDOX TRANSFORMATION OF ADDUCTS FROM CYCLOADDITION OF DIAZOACETIC ESTER TO β-ARYLACRYLOYLOXIRANES

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It was established that, in addition to ethyl 4-aryl-3-(2,3-epoxyalkanoyl)-4,5-dihydro-1H-pyrazole-5-carboxylates, the reaction of diazoacetic ester with β-arylacryloyloxiranes also gives ethyl 4-aryl-3(5)-(3-hydroxy-2-methylalkanoyl)-1H-pyrazole-5(3)-carboxylates. The latter are formed from the tautomeric ethyl 4-aryl-5-(2,3-epoxyalkanoyl)-4,5-dihydro-1H-pyrazole-3-carboxylates as a result of intramolecular oxidative–reductive disproportionation.

Keywords: β-arylacryloyloxiranes, diazoacetic ester, 4,5-dihydro-1H-pyrazoles, 1,3-dipolar cycloaddition, spectral characteristics.

The cycloaddition of diazomethane to β-arylacryloyloxiranes, leading to the formation of 4-aryl-3-(2-methyl-2,3-epoxypropionyl)-4,5-dihydro-1H-pyrazoles, has been investigated systematically [1]. The formation of a mixture of two diastereomeric *trans*-4,5-dihydro-1H-pyrazole-5-carboxylates and in some cases a third substance, which was tentatively assigned the structure of the *cis* isomer, was detected [2].

In order to extend the range of substituted epoxyalkanoyl-4,5-dihydro-1H-pyrazoles as synthons for the structural analogs of the alkaloid vitasomnine and to determine the structure of the minor adducts formed in the reaction we continued investigations into the cycloaddition of diazoacetic ester to β-arylacryloyloxiranes. By heating the β-acryloyloxiranes **1a-i** with diazoacetic ester in dioxane for 7-20 h we obtained 30-72% yields of ethyl 4-aryl-3-(2-methyl-2,3-epoxyalkanoyl)-4,5-dihydro-1H-pyrazole-5-carboxylates **2a-i** (Scheme 1) as mixtures of two diastereomers (~1:1), differing in the relative configuration of the chiral center of the oxirane ring. During chromatographic separation of the mother solutions after isolating the 4,5-dihydro-1H-pyrazoles **2a-e**,**g**,**i** we obtained 5-28% yields of previously unidentified [2] ethyl 4-aryl-3(5)-(3-hydroxyalkanoyl)-1H-pyrazole-5(3)-carboxylates **3a-e**,**g**,**i**. Compounds **3a-e**,**g** were individual compounds, while the pyrazole **3i** was isolated in the form of a diastereomeric mixture (1:1). In the reaction of compounds **1f**,**h** with diazoacetic ester the presence of the pyrazoles **3f**,**h** in the reaction mixture was demonstrated by TLC and ^{1}H NMR spectroscopy.

The structures of the obtained compounds **2a-i** and **3a-i** were confirmed by data from elemental analysis and IR and ^{1}H NMR spectra (Tables 1 and 2). Thus, the IR spectra of compounds **2a-i** contain bands for the stretching vibrations of the carbonyl and ester C=O groups in the regions of 1645-1659 and 1744-1750 cm^{-1} [3]. In the ^{1}H NMR spectra of compounds **2a-i** there are two AB spin systems of signals for the vicinal protons of the 4,5-dihydro-1H-pyrazole ring and the geminal protons of the epoxide ring,* a quartet and triplet for the ethyl

* In the case of **2i** a doublet for the protons of the methyl group and a quartet for the methine proton.

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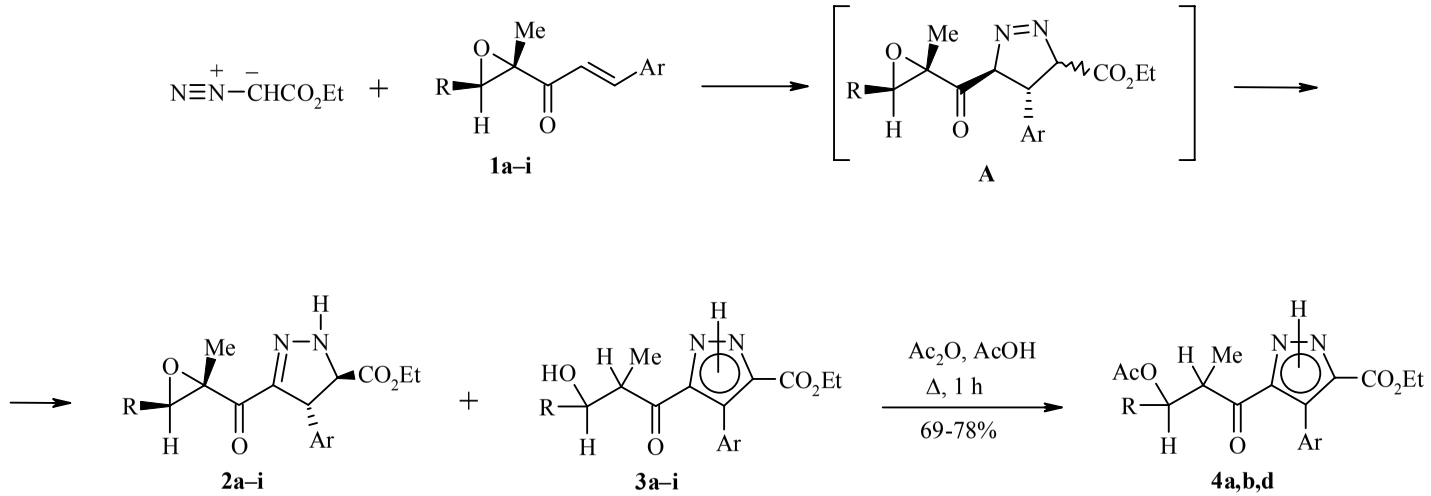
Scheme 1



1–4 a–h R = H, **i** R = Me; **a**, **i** Ar = Ph, **b** Ar = 4-BrC_6H_4, **c** Ar = 4-ClC_6H_4, **d** Ar = 4-FC_6H_4, **e** Ar = 4-$O_2NC_6H_4$, **f** Ar = 4-$MeOC_6H_4$, **g** Ar = 3-BrC_6H_4, **h** Ar = 3-$O_2NC_6H_4$

TABLE 1. The Characteristics of Compounds **2c**,**d**,**f**,**i**, **3a-e**,**g**,**i**, and **4a**,**b**,**d***

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2c	$C_{16}H_{17}ClN_2O_4$	57.26 / 57.06	5.18 / 5.09	8.43 / 8.32	126-128	49
2d	$C_{16}H_{17}FN_2O_4$	60.21 / 59.99	5.57 / 5.35	8.88 / 8.75	125-128	55
2f	$C_{17}H_{20}N_2O_5$	61.49 / 61.44	6.26 / 6.07	8.56 / 8.43	122-123	30
2i	$C_{17}H_{20}N_2O_4$	64.29 / 64.54	6.40 / 6.37	9.03 / 8.86	143-145	54
3a	$C_{16}H_{18}N_2O_4$	63.68 / 63.56	6.12 / 6.00	9.40 / 9.27	125-127	28
3b	$C_{16}H_{17}BrN_2O_4$	50.20 / 50.41	4.31 / 4.49	7.49 / 7.35	142-145	28
3c	$C_{16}H_{17}ClN_2O_4$	57.30 / 57.06	5.22 / 5.09	8.48 / 8.32	136-137	22
3d	$C_{16}H_{17}FN_2O_4$	60.18 / 59.99	5.46 / 5.35	8.92 / 8.75	128-129	18
3e	$C_{16}H_{17}N_3O_6$	55.12 / 55.33	4.74 / 4.93	12.27 / 12.10	172-173	25
3g	$C_{16}H_{17}BrN_2O_4$	50.22 / 50.41	4.40 / 4.49	7.50 / 7.35	123-125	26
3i	$C_{17}H_{20}N_2O_4$	64.35 / 64.54	6.52 / 6.37	9.05 / 8.86	Oil	5
4a	$C_{18}H_{20}N_2O_5$	62.51 / 62.78	5.73 / 5.85	8.31 / 8.13	Oil	78
4b	$C_{18}H_{19}BrN_2O_5$	51.19 / 51.08	4.64 / 4.52	6.79 / 6.62	Oil	71
4d	$C_{18}H_{19}FN_2O_5$	59.84 / 59.66	5.50 / 5.29	7.90 / 7.73	Oil	69

* The characteristics of compounds **2a**,**b**,**e**,**g**,**h** were described in [2].

TABLE 2. The Spectral Characteristics of Compounds **2c**,**d**,**f**,**i**, **3a-e**,**g**,**i** and **4a**,**b**,**d***

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)*[2]
1	2	3
2c	3261, 1744, 1645	*1* 8.50 (1H, br. s, NH), 7.55 (2H, d, *J* = 8.7, H_{Ar}-3',5'), 7.11 (2H, d, *J* = 8.7, H_{Ar}-2',6'), 4.70 (1H, d, *J* = 4.0, H-4), 4.33 (1H, d, *J* = 4.0, H-5), 4.23 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$), 3.08 (1H, d, *J* = 5.5, H_{ep}), 2.82 (1H, d, *J* = 5.5, H_{ep}), 1.60 (3H, s, CH_{3ep}), 1.30 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$)
		2 8.50 (1H, br. s, NH), 7.55 (2H, d, *J* = 8.7, H_{Ar}-3',5'), 7.11 (2H, d, *J* = 8.7, H_{Ar}-2',6'), 4.68 (1H, d, *J* = 4.0, H-4), 4.32 (1H, d, *J* = 4.0, H-5), 4.23 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$), 3.26 (1H, d, *J* = 5.5, H_{ep}), 2.81 (1H, d, *J* = 5.5, H_{ep}), 1.60 (3H, s, CH_{3ep}), 1.30 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$)
2d	3256, 1748, 1650	*1* 7.10 (2H, dd, *J* = 9.0, $^4J_{HF}$ = 5.8, H_{Ar}-2',6'), 7.00 (2H, dd, *J* = 9.0, $^3J_{HF}$ = 9.0, H_{Ar}-3',5'), 6.90 (1H, br. s, NH), 4.66 (1H, d, *J* = 3.9, H-4), 4.27 (1H, d, *J* = 3.9, H-5), 4.24 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$), 3.07 (1H, d, *J* = 5.5, H_{ep}), 2.82 (1H, d, *J* = 5.5, H_{ep}), 1.60 (3H, s, CH_{3ep}), 1.30 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$)
		2 7.10 (2H, dd, *J* = 9.0, $^4J_{HF}$ = 5.8, H_{Ar}-2',6'), 7.00 (2H, dd, *J* = 9.0, $^3J_{HF}$ = 9.0, H_{Ar}-3',5'), 6.90 (1H, br. s, NH), 4.64 (1H, d, *J* = 4.0, H-4), 4.24 (1H, d, *J* = 4.0, H-5), 4.24 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$), 3.26 (1H, d, *J* = 5.5, H_{ep}), 2.80 (1H, d, *J* = 5.5, H_{ep}), 1.58 (3H, s, CH_{3ep}), 1.30 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$)

TABLE 2 (continued)

1	2	3
2f	3296, 1752, 1650	*1* 7.10 (2H, d, J = 8.6, H_{Ar}-2',6'), 6.99 (1H, br. s, NH), 6.81 (2H, d, J = 8.6, H_{Ar}-3',5'), 4.63 (1H, d, J = 3.8, H-4), 4.27 (1H, d, J = 3.8, H-5), 4.23 (2H, q, J = 7.1, $C\underline{H}_2CH_3$), 3.76 (3H, s, OCH_3), 3.05 (1H, d, J = 5.5, H_{ep}), 2.80 (1H, d, J = 5.5, H_{ep}), 1.60 (3H, s, CH_{3ep}), 1.22 (3H, t, J = 7.1, $CH_2C\underline{H}_3$)
		2 7.10 (2H, d, J = 8.6, H_{Ar}-2',6'), 6.99 (1H, br. s, NH), 6.81 (2H, d, J = 8.6, H_{Ar}-3',5'), 4.60 (1H, d, J = 3.7, H-4), 4.24 (1H, d, J = 3.7, H-5), 4.23 (2H, q, J = 7.1, $C\underline{H}_2CH_3$), 3.76 (3H, s, OCH_3), 3.25 (1H, d, J = 5.5, H_{ep}), 2.80 (1H, d, J = 5.5, H_{ep}), 1.60 (3H, s, CH_{3ep}), 1.22 (3H, t, J = 7.1, $CH_2C\underline{H}_3$)
2i	3261, 1750, 1649	*1* 7.15-7.35 (5H, m, C_6H_5), 7.01 (1H, br. s, NH), 4.63 (1H, d, J = 4.1, H-4), 4.28 (1H, d, J = 4.1, H-5), 4.23 (2H, q, J = 7.1, $C\underline{H}_2CH_3$), 3.27 (1H, q, J = 5.2, H_{ep}), 1.54 (3H, s, CH_{3ep}), 1.35 (3H, d, J = 5.2, CH_{3ep}), 1.30 (3H, t, J = 7.1, $CH_2C\underline{H}_3$)
		2 7.15-7.35 (5H, m, C_6H_5), 7.01 (1H, br. s, NH), 4.67 (1H, d, J = 4.1, H-4), 4.31 (1H, d, J = 4.1, H-5), 4.23 (2H, q, J = 7.1, $C\underline{H}_2CH_3$), 3.15 (1H, q, J = 5.2, H_{ep}), 1.53 (3H, s, CH_{3ep}), 1.35 (3H, d, J = 5.2, CH_{3ep}), 1.30 (3H, t, J = 7.1, $CH_2C\underline{H}_3$)
3a	3340, 3140, 1710, 1670	7.30-7.45 (5H, m, C_6H_5), 4.24 (2H, q, J = 7.0, $C\underline{H}_2CH_3$), 3.84 (1H, br. dd, J = 7.3, J = 11.0, $C\underline{H}HOH$), 3.71 (1H, br. dd, J = 3.8, J = 11.0, $CH\underline{H}OH$), 3.52-3.70 (2H, m, $C\underline{H}CH_3$, OH), 1.15 (3H, t, J = 7.0, $CH_2C\underline{H}_3$), 1.15 (3H, d, J = 6.3, $CHC\underline{H}_3$)
3b	3345, 3140, 1711, 1673	7.42 (2H, d, J = 8.7, H_{Ar}-3',5'), 7.12 (2H, d, J = 8.7, H_{Ar}-2',6'), 4.22 (2H, q, J = 7.0, $C\underline{H}_2CH_3$), 3.86 (1H, br. dd, J = 7.1, J = 11.0, $C\underline{H}HOH$), 3.73 (1H, br. dd, J = 4.0, J = 11.0, $CH\underline{H}OH$), 3.50-3.70 (2H, m, $C\underline{H}CH_3$, OH), 1.15 (3H, t, J = 7.0, $CH_2C\underline{H}_3$), 1.15 (3H, d, J = 6.2, $CHC\underline{H}_3$)
3c	3346, 3142, 1710, 1671	7.45 (2H, d, J = 8.6, H_{Ar}-3',5'), 7.13 (2H, d, J = 8.6, H_{Ar}-2',6'), 4.22 (2H, q, J = 7.0, $C\underline{H}_2CH_3$), 3.85 (1H, br. dd, J = 7.1, J = 11.0, $C\underline{H}HOH$), 3.73 (1H, br. dd, J = 4.0, J = 11.0, $CH\underline{H}OH$), 3.50-3.70 (2H, m, $C\underline{H}CH_3$, OH), 1.15 (3H, t, J = 7.0, $CH_2C\underline{H}_3$), 1.15 (3H, d, J = 6.2, $CHC\underline{H}_3$)
3d	3349, 3141, 1712, 1670	7.29 (2H, dd, J = 9.0, $^4J_{HF}$ = 5.6, H_{Ar}-2',6'), 7.06 (2H, dd, J = 9.0, $^3J_{HF}$ = 9.0, H_{Ar}-3',5'), 4.22 (2H, q, J = 7.2, $C\underline{H}_2CH_3$), 3.87 (1H, br. dd, J = 8.5, J = 12.0, $C\underline{H}HOH$), 3.71 (1H, br. dd, J = 4.0, J = 12.0, $CH\underline{H}OH$), 3.50-3.75 (2H, m, $C\underline{H}CH_3$, OH), 1.15 (3H, t, J = 7.2, $CH_2C\underline{H}_3$), 1.14 (3H, d, J = 6.6, $CHC\underline{H}_3$)
3e	3345, 3140, 1710, 1675	8.17 (2H, d, J = 8.7, H_{Ar}-3',5'), 7.59 (2H, d, J = 8.7, H_{Ar}-2',6'), 4.22 (2H, q, J = 7.1, $C\underline{H}_2CH_3$), 3.86 (1H, br. dd, J = 7.6, J = 11.5, $C\underline{H}HOH$), 3.72 (1H, br. dd, J = 4.0, J = 11.5, $CH\underline{H}OH$), 3.50-3.74 (2H, m, $C\underline{H}CH_3$, OH), 1.15 (3H, t, J = 7.1, $CH_2C\underline{H}_3$), 1.15 (3H, d, J = 6.2, $CHC\underline{H}_3$)
3g	3345, 3140, 1710, 1675	7.10-7.49 (4H, m, H_{Ar}), 7.10-7.49 (4H, m, H_{Ar}), 4.22 (2H, q, J = 7.1, $C\underline{H}_2CH_3$), 3.85 (1H, br. dd, J = 7.9, J = 11.1, $C\underline{H}HOH$), 3.73 (1H, br. dd, J = 4.0, J = 11.1, $CH\underline{H}OH$), 3.50-3.75 (2H, m, $C\underline{H}CH_3$, OH), 1.15 (3H, d, J = 6.2, $CHC\underline{H}_3$), 1.15 (3H, t, J = 7.1, $CH_2C\underline{H}_3$)
3i	3380, 3160, 1708, 1680	*1* 7.20-7.49 (5H, m, C_6H_5), 4.22 (2H, q, J = 7.1, $C\underline{H}_2CH_3$), 4.01 (1H, dq, J = 6.4, J = 7.1, $C\underline{H}(CH_3)OH$), 3.42 (1H, dq, J = 7.1, J = 7.1, $C\underline{H}CH_3$), 1.18 (3H, d, J = 6.4, $CHC\underline{H}_3$), 1.15 (3H, d, J = 7.1, $CHC\underline{H}_3$), 1.11 (3H, t, J = 7.1, $CH_2C\underline{H}_3$)
		2 7.20-7.49 (5H, m, C_6H_5), 4.22 (2H, q, J = 7.1, $C\underline{H}_2CH_3$), 4.16 (1H, dq, J = 3.0, J = 6.4, $C\underline{H}HOH$), 3.37 (1H, dq, J = 3.0, J = 7.1, $C\underline{H}CH_3$), 1.18 (3H, d, J = 6.4, $CHC\underline{H}_3$), 1.15 (3H, d, J = 7.1, $CHC\underline{H}_3$), 1.13 (3H, t, J = 7.1, $CH_2C\underline{H}_3$)
4a	3160, 1735, 1709, 1677	7.20-7.50 (6H, m, C_6H_5, NH), 4.28 (1H, dd, J = 7.5, J = 12.0, $CH\underline{H}OAc$), 4.23 (2H, q, $C\underline{H}_2CH_3$), 4.16 (1H, dd, J = 5.1, J = 12.0, $C\underline{H}HOAc$), 3.65-3.90 (1H, m, $C\underline{H}CH_3$), 1.96 (3H, s, $COCH_3$), 1.14 (3H, t, J = 7.1, $CH_2C\underline{H}_3$), 1.13 (3H, d, J = 6.6, $CHC\underline{H}_3$)
4b	—	7.44 (2H, d, J = 8.6, H_{Ar}-3',5'), 7.11 (2H, d, J = 8.6, H_{Ar}-2',6'), 4.04-4.45 (4H, m, $C\underline{H}_2OAc$, $C\underline{H}_2CH_3$), 3.49-3.92 (1H, m, $C\underline{H}CH_3$), 1.97 (3H, s, $COCH_3$), 1.14 (3H, t, J = 7.0, $CH_2C\underline{H}_3$), 1.12 (3H, d, J = 6.6, $CHC\underline{H}_3$)
4d	—	7.10 (2H, dd, J = 9.0, $^4J_{HF}$ = 5.9, H_{Ar}-2',6'), 7.07 (2H, dd, J = 9.0, $^3J_{HF}$ = 9.0, H_{Ar}-3',5'), 4.04-4.45 (4H, m, $C\underline{H}_2OAc$, $C\underline{H}_2CH_3$), 3.51-3.90 (1H, m, $C\underline{H}CH_3$), 1.97 (3H, s, $COCH_3$), 1.14 (3H, t, J = 7.0, $CH_2C\underline{H}_3$), 1.12 (3H, d, J = 6.6, $CHC\underline{H}_3$)

* The characteristics of compounds **2a**,**b**,**e**,**g**,**h** were described in [2].

*[2] *1* – Diastereomer 1; *2* – diastereomer 2.

protons of the ester group with a spin–spin coupling constant of 7.1-7.2 Hz, and downfield signals for the protons of the aromatic ring and the NH protons. The transoid orientation of the ester group and the aromatic ring in the pyrazole ring of the diastereomers **2a-i** are confirmed by the spin–spin coupling constants of the vicinal protons (J = 3.9-4.9 Hz) and also by data from the Overhauser effect [2].

In the IR spectra of compounds **3a-e**,**g**,**i** there are bands for the stretching vibrations of the C=O bonds of the carbonyl and ester groups in the region of 1670-1680 and 1708-1712 cm^{-1}, indicating that they are conjugated with the pyrazole ring. The stretching vibrations of the NH bond appear in the form of a characteristic band at 3140-3180 cm^{-1}, while the band in the region of 3340-3380 cm^{-1} indicates the presence of a hydroxyl group. In the ^{1}H NMR spectra of the ethyl pyrazolecarboxylates **3a-i** there are signals for the characteristic system of bonded protons of the ethyl group in the form of a triplet with J = 7.1 Hz at 1.15 ppm and a quartet at 4.42 ppm, while the appearance of a doublet for the protons of the methyl group with J = 6.3 Hz at 1.15-1.25 ppm (two doublets in the case of compound **3i**) confirms the reductive opening of the epoxide ring. The form of the signals for the methylene protons previously belonging to the oxirane ring, changes substantially as a result of its opening, i.e., the signal of each of these protons appears in the ^{1}H NMR spectra of the pyrazoles **3a-h** in the form of a doublet of doublets at 3.71-3.73 ppm (J_{gem} = 11.0-12.0, J_{vic} = 3.8-4.0) and 3.84-3.87 (J_{gem} = 11.0-12.0, J_{vic} = 7.1-8.5 Hz). The signal of the methine proton is masked by a broad signal for the proton of the hydroxyl group at 3.50-3.75 ppm. In compound **3i** as a result of reductive opening of the oxirane ring signals for the two methine protons appear in the form of a pair of doublets of quartets.

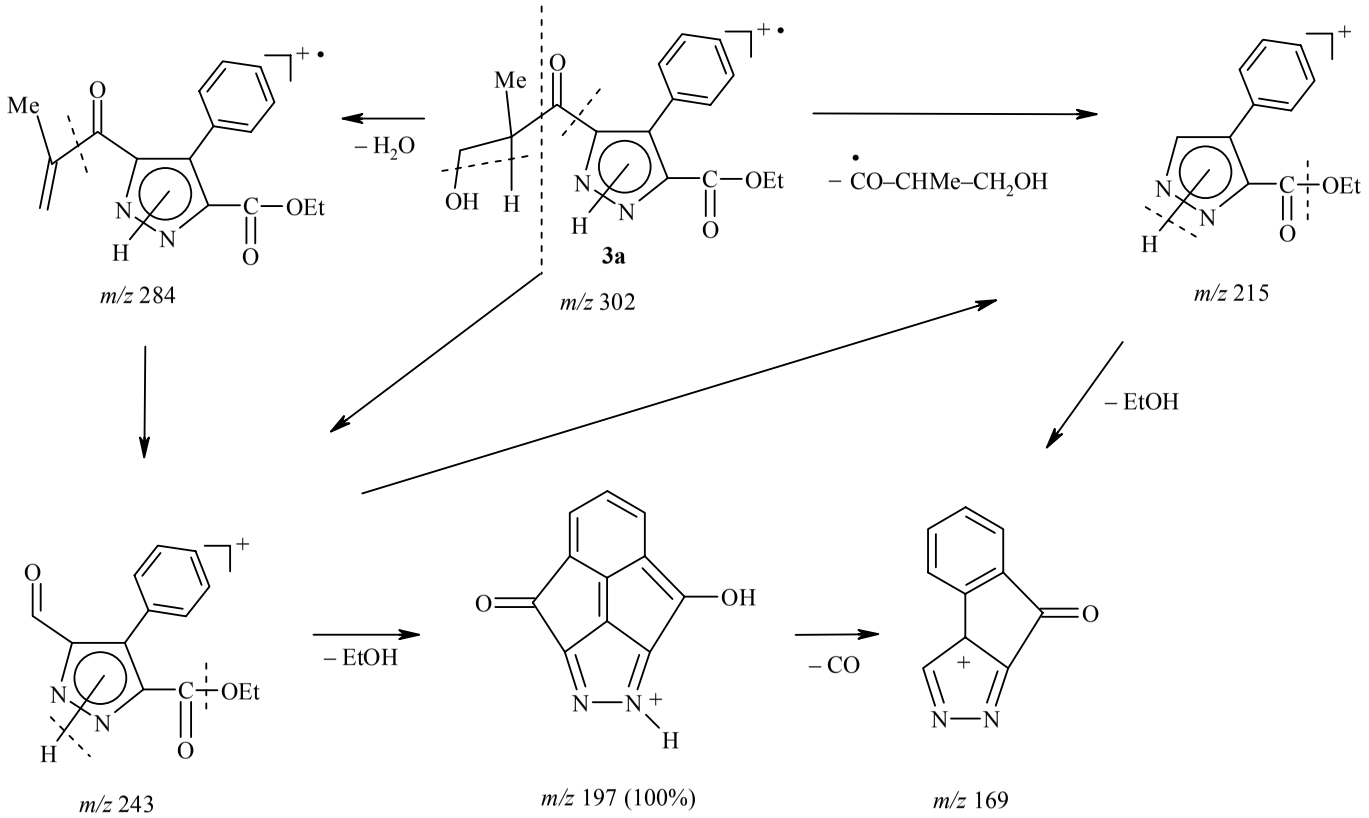
A characteristic feature of the mass spectrum of compound **3a** is the low intensity of the molecular ion peak m/z 302 and the presence of a peak for the radical-ion with m/z 284, due to the elimination of a water molecule $[M - H_2O]^{+\cdot}$ (Scheme 2). The peak with the highest intensity belongs to the diacylphenylpyrazole fragment with m/z 197, the increased stability of which is due to the ability to form a conjugated cyclic ion.

The presence of a free hydroxyl group was also confirmed by acetylation of the β-hydroxypropionyl-1H-pyrazolecarboxylates **3a**,**b**,**d** with acetic anhydride. In the ^{1}H NMR spectra of the ethyl 4-aryl-3(5)-(3-acetoxy-2-methylpropionyl)-1H-pyrazole-5(3)-carboxylates **4a**,**b**,**d** a singlet appears for the protons of the acetyl group, and a downfield shift of the signals for the protons of the methylene group is also observed.

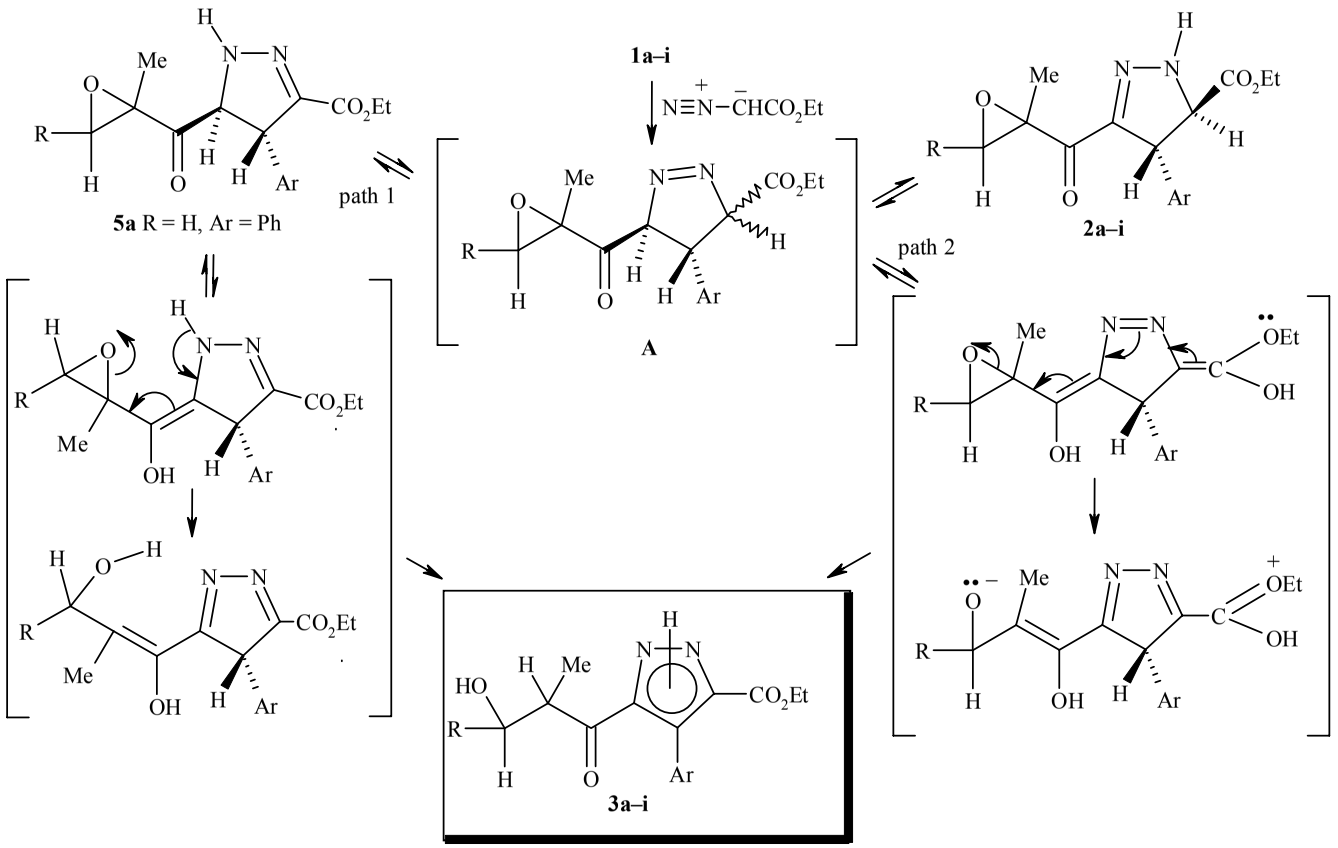
In order to identify the precursors of the β-hydroxyalkanoyl-1H-pyrazolecarboxylates **3a-h** and to confirm their regioisomeric affiliation to the series of 1H-pyrazole-3(5)-carboxylate esters the diastereomeric mixture of adducts **2a** was heated in dioxane in a sealed tube. Detection of the β-hydroxypropionyl-1H-pyrazole **3a** in significantly smaller amounts (not more than 3%) than in the reaction of the enone **1a** with diazoacetic ester after heating compound **2a** for 10 h indicates that 4,5-dihydro-1H-pyrazole **2a** is not the direct precursor of the pyrazole **3a**, although these substances are clearly formed from one intermediate 4,5-dihydro-3H-pyrazole (**A**), which is the adduct from reaction of diazoacetic ester and the epoxyenone with the 1,3-dipole oriented according to the Auwers rule. Moreover, by detailed analysis of the ^{1}H NMR spectrum of the reaction mixture of the enone **1a** with diazoacetic ester after boiling for 3 h it was possible to detect the formation of ethyl 5-(2-methyl-2,3-epoxypropionyl)-4-phenyl-4,5-dihydro-1H-pyrazole-3-carboxylates **5a** (Scheme 3), formed as a result of displacement of a proton from the carbon atom attached to the ester group in the initial adduct **A**, in addition to the previously isolated diastereomers **2a** tautomeric with them. The decrease in the content of compounds **5a** with the simultaneous increase of the β-hydroxypropionyl-1H-pyrazole **3a** when the reaction mixture is heated indicates that they are formed during intramolecular oxidation–reduction disproportionation of compounds **5a**, and this made it possible to propose the following mechanism for the transformation.

According to this mechanism, the rearrangement may take place synchronously through a six-membered transition state, the formation of which is preceded by migration of a proton to the nitrogen atom from the α-position in relation to the ester group and enolization of the acyl substituent, while a subsequent 1,5-sigmatropic shift leads to intramolecular oxidative–reductive disproportionation (path 1). Reductive opening of the oxirane ring may also be realized as a result of displacement of the electron pair involving the oxygen atom of the ester group through the intermediate azodienol (path 2), the formation of which also presupposes the presence of mobile hydrogen atoms at positions 3 and 5 of the intermediate 4,5-dihydro-3H-pyrazole **A**.

Scheme 2

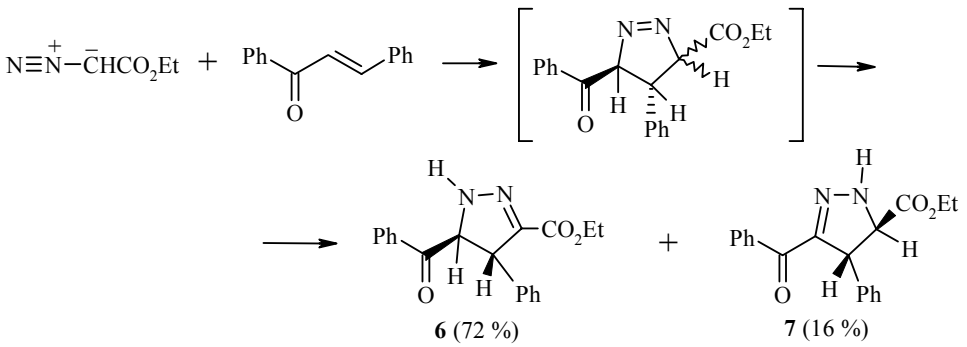

Me
O
N
N
H
C—OEt
O
– H2O
OH
H
3a
– CO–CHMe–CH2OH
m/z 284
m/z 302
m/z 215
– EtOH
– EtOH
– CO
OH
m/z 243
m/z 197 (100%)
m/z 169

Scheme 3



To compare the probability of migration of a proton from the α positions to the ester and carbonyl groups in the analogs of 1,3-disubstituted 4,5-dihydro-1H-pyrazoles, which are not capable of rearrangement, 1,3-diphenylprop-2-en-1-one was reacted with diazoacetic ester. The reasons for investigation of this reaction were not only to simplify the stereochemical composition of the adducts compared with the studied enones but also to resolve the existing contradiction in the literature about the interpretation of the structure of the adducts from the cycloaddition of diazoacetic ester to chalcones [5-9]. It was established that the reaction of 1,3-diphenylprop-2-en-1-one with diazoacetic ester by boiling in dioxane leads to a mixture of two 4,5-dihydro-1H-pyrazoles **6** and **7** (4.5:1) with the transoid arrangement of the substituents in the azole ring (J_{vic} = 3.7-3.9 Hz) (Scheme 4).

Scheme 4



6 (72 %) **7** (16 %)

On the basis of comparison of the chemical shifts of the vicinal protons of the 4,5-dihydro-1H-pyrazole ring and the character and form of the multiplets for the methylene protons of the ethyl group the structure of ethyl 5-benzoyl-4-phenyl-4,5-dihydro-1H-pyrazole-3-carboxylate (**6**) was assigned to the isomer formed in the larger amount, and 3-benzoyl-4-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**7**) to the isomer in the smaller amount. This assignment was also confirmed in the IR spectra of compound **6** by the low-frequency shift of the bands for the stretching vibrations of the C=O bond of the ester group to 1707 cm^{-1} as a result of conjugation [6].

A characteristic feature of the ^{1}H NMR spectra of compounds **6** and **5a** is the form of the signals for the methylene protons of the ethyl group, each of which represents a doublet of quartets (quartets in compounds **7** and **2a**). It is clear that the formation of a mixture of isomeric 4,5-dihydro-1H-pyrazoles **6** and **7** in this reaction confirms the possibility of the dual migration of protons from positions 3 and 5 of the initial 4,5-dihydro-3H-pyrazole that is necessary for realization of the redox transformation.

In the general case, the intramolecular reductive opening of the oxirane ring and oxidation of the azole ring represent a vinylogous rearrangement of the epoxides into allyl groups, of which is favored by subsequent aromatization of the carbocyclic [10] or heterocyclic, as in our case, rings.

EXPERIMENTAL

The IR spectra were obtained on a Specord IR-75 spectrometer in tablets with potassium bromide. The ^{1}H NMR spectra were recorded on Bruker AC-200 (200 MHz) and Bruker AVANCE (400 MHz) spectrometers in deuterochloroform with HMDS as internal standard (δ 0.055 ppm). The mass spectra were obtained on a Shimadzu QP-5000 instrument with 70-eV ionizing electrons.

The reactions and the individuality of the obtained compounds were monitored by TLC on Silufol and Kieselgel 60 F_{254} plates with 1:1-1:5 diethyl ether–hexane as eluant and iodine vapor or 4% $KMnO_4$ solution as developer. The initial β-arylacryloyloxiranes **1a-i** were obtained by the condensation of the respective

acyloxiranes and aromatic aldehydes in methanol in the presence of a 15% methanol solution of sodium hydroxide [11]. The diazoacetic ester was synthesized by the method in [12].

The characteristics of compounds **2c**,**d**,**f**,**i**, **3a-e**,**g**,**i**, and **4a**,**b**,**d** are given in Tables 1 and 2, and those of compounds **2a**,**b**,**e**,**g**,**h** were described earlier [2].

Ethyl 4-Aryl-3-(2,3-epoxyalkanoyl)-4,5-dihydro-1H-pyrazole-5-carboxylates 2a-i and Ethyl 4-Aryl-3(5)-(3-hydroxy-2-methylalkanoyl)-1H-pyrazole-5(3)-carboxylates 3a-i. To a solution of diazoacetic ester (5.81 g, 51 mmol) in dioxane (60 ml) we added the respective β-arylacryloyloxirane **1a-i** (50 mmol). The mixture was heated at 80-90°C with a reflux condenser for 7-20 h. The heating was stopped when the initial epoxyenone had disappeared according to TLC. The dioxane was evaporated under vacuum, and the diastereomeric mixtures of compounds **2a-i** crystallized from the residue after the addition of diethyl ether or a mixture of diethyl and petroleum ethers. In the case of the reaction mixtures from compounds **1a-e**,**g**,**i** with diazoacetic ester the mother solutions after removal of the solvent were submitted to column chromatography on silica gel with linear gradient elution with mixtures of diethyl ether and petroleum ether (1:1) and diethyl ether. Compounds **3a-e**,**g**,**i**, which had the lowest chromatographic mobility, crystallized from the final fractions.

Compound 3a. Mass spectrum, *m*/*z* (I_{rel}, %): 302 $[M]^+$ (12), 284 $[M^+–18]$ (0.5), 273 (11), 272 (11), 260 (11), 243 (19), 227 (18), 215 (6), 197 (100), 171 (6), 169 (8), 142 (21), 141 (24), 129 (13), 115 (31), 113 (34), 80 (16).

Compounds **3f**,**h** were detected in the ^{1}H NMR spectra of the reaction mixtures.

Compound 3f. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.24 (2H, d, *J* = 8.6, H_{Ar}-2',6'); 7.00 (1H, br. s, NH); 6.82 (2H, d, *J* = 8.6, H_{Ar}-3',5'); 4.24 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 3.84 (1H, br. dd, *J* = 7.3, *J* = 11.0, $C\underline{H}HOH$); 3.77 (3H, s, OCH_3); 3.71 (1H, br. dd, *J* = 3.8, *J* = 11.0, $CH\underline{H}OH$); 3.52-3.70 (2H, m, $C\underline{H}CH_3$, OH); 1.15 (3H, d, *J* = 6.3, $CHC\underline{H}_3$).

Compound 3h. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.60-8.20 (4H, m, HAr); 4.24 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 3.84 (1H, br. dd, *J* = 7.3, *J* = 11.0, $C\underline{H}HOH$); 3.72 (1H, br. dd, *J* = 3.8, *J* = 11.0, $CH\underline{H}OH$); 3.52-3.70 (2H, m, $C\underline{H}CH_3$, OH); 1.15 (3H, d, *J* = 6.3, $CHC\underline{H}_3$); 1.15 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$).

Ethyl 5-(2-Methyl-2,3-epoxypropionyl)-4-phenyl-4,5-dihydro-1H-pyrazole-3-carboxylates (5a). These compounds were detected in the ^{1}H NMR spectra of samples of the reaction mixtures taken after boiling for 3 and 10 h under the conditions described above. ^{1}H NMR spectrum, δ, ppm (*J*, Hz). Diastereomer 1: 7.20-7.40 (5H, m, C_6H_5); 6.77 (1H, br. s, HN); 4.77 (1H, d, *J* = 6.4, CH_{pyraz}); 4.17 (1H, dq, *J* = 7.1, *J* = 11.0, $CH\underline{H}CH_3$); 4.14 (1H, dq, *J* = 7.1, *J* = 11.0, $C\underline{H}HCH_3$); 2.97 (1H, d, *J* = 4.4, CH_{ep}); 1.60 (3H, s, CH_3); 2.92 (1H, d, *J* = 4.4, CH_{ep}); 1.18 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). Diastereomer 2: 7.20-7.40 (5H, m, C_6H_5); 6.65 (1H, br. s, NH); 4.49 (1H, d, *J* = 4.2, CH_{pyraz}); 4.31 (1H, d, *J* = 4.2, CH_{pyraz}); 4.15 (1H, dq, *J* = 7.1, *J* = 11.0, $CH\underline{H}CH_3$); 4.12 (1H, dq, *J* = 7.1, *J* = 11.0, $CH\underline{H}CH_3$); 2.90 (1H, d, *J* = 4.6, CH_{ep}); 2.87 (1H, d, *J* = 4.6, CH_{ep}); 1.56 (3H, s, CH_3); 1.21 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$)

Ethyl 4-Aryl-3(5)-(3-acetoxy-2-methylpropionyl)-1H-pyrazole-5(3)-carboxylates 4a,b,d. To β-hydroxypropionylpyrazoles **3a**,**b**,**d** (5 mmol) we added acetic anhydride (1 ml, 11 mmol) in acetic acid (2.5 ml), and we boiled the mixture for 1 h. The mixture was diluted with twice the volume of water, neutralized with an aqueous solution of sodium carbonate, and extracted with diethyl ether (3 × 25 ml). After drying over sodium sulfate the ether was evaporated, and the isolated oil was chromatographed on silica gel with ether as eluant. The acetates **4a**,**b**,**d** were oily substances.

Ethyl 5-Benzoyl-4-phenyl-4,5-dihydro-1H-pyrazole-3-carboxylate (6) and Ethyl 4,5-dihydro-1H-pyrazole-5-carboxylate (7). To a solution of 1,3-diphenylprop-2-en-1-one (5.2 g, 25 mmol) in dioxane (40 ml) we added diazoacetic ester (2.96 g, 26 mmol). The mixture was boiled with a reflux condenser for 4 h. The solvent was evaporated under vacuum, and the residue was crystallized from diethyl ether. We obtained 2.9 g of 4,5-dihydro-1H-pyrazole **6**. The residue was chromatographed on silica gel with linear gradient elution with mixtures of diethyl ether and petroleum ether (1:1) and diethyl ether. We obtained a further 3.0 g of compound **6** (mp 161-162°C, from 1:2 petroleum ether and ether, published data 162°C [7], 165°C [6]) (total yield 72%) and 1.3 g (16%) of compound **7** in the form of an oil.

Compound 6. IR spectrum, ν, cm^{-1}: 1707 ($C=O_{ester}$), 1680 ($C=C_{keto}$). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.86 (2H, dd, *J* = 1.0, *J* = 8.3, H_{Ph}-2',6'); 7.63 (1H, tt, *J* = 1.0, *J* = 7.4, H_{Ph}-4'); 7.48 (2H, dd, *J* = 7.4, *J* = 8.3, H_{Ph}-3',5'); 7.30-7.42 (5H, m, C_6H_5); 7.00 (1H, br. s, NH); 5.19 (1H, d, *J* = 3.9, H-5); 4.46 (1H, d, *J* = 3.9, H-4); 4.16 (1H, dq, *J* = 7.1, *J* = 10.5, $CH\underline{H}CH_3$); 4.10 (1H, dq, *J* = 7.1, *J* = 10.5, $C\underline{H}HCH_3$); 1.20 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). Found %: C 70.75; H 5.58; N 8.88. $C_{19}H_{18}N_2O_3$. Calculated %: C 70.79; H 5.63; N 8.69.

Compound 7. IR spectrum, ν, cm^{-1}: 1720 ($C=O_{est}$), 1660 ($C=C_{keto}$), 3320 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.10 (2H, m, H_{PhCO}-2',6'); 7.30-7.50 (8H, m, $5H_{Ph-C}$, $3H_{PhCO}$-3',4',5'); 7.02 (1H, br. s, NH); 4.90 (1H, d, *J* = 3.7, H-5); 4.36 (1H, d, *J* = 3.7, H-4); 4.26 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 1.31 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). Found %: C 70.92; H 5.80; N 8.94. $C_{19}H_{18}N_2O_3$. Calculated %: C 70.79; H 5.63; N 8.69.

Heating of Ethyl 3-(2-Methyl-2,3-epoxypropionyl)-4-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate (2a) in Dioxane. A solution of the diastereomeric 4,5-dihydro-1H-pyrazoles **2a** (0.6 g, 2.0 mmol) in dioxane (5 ml) was heated in a sealed tube at 85-90°C for 10 h. The presence of the pyrazole **3a** was detected during analysis of the reaction mixture by ^1H NMR spectroscopy.

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