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Reaction of 4,5-Dihydro-1*H*-pyrazole-3,5,5-tricarboxylic Acids Esters with Halogens

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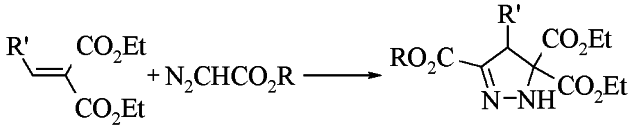
Abstract—Esters of 4-R-4,5-dihydro-1*H*-pyrazole-3,5,5-tricarboxylic acids with chlorine yield esters of 4-R-5-chloro-4,5-dihydro-3H-pyrazole-3,3,5-tricarboxylic acids that at thermolysis provide the esters of the corresponding 2-chlorocyclopropanetricarboxylic acid. The same esters react with bromine in dichloromethane at room temperature to give a mixture of esters of the corresponding 1*H*-pyrazole-3,5-dicarboxylic acids and 5-bromo-4,5-dihydro-3,3,5-tricarboxylic acids. From 5,5-diethyl 3-methyl 4,5-dihydro-1*H*-pyrazole-3,5,5-tricarboxylate and *N*-iodosuccinimide or a system iodine—silver trifluoroacetate we obtained 1,1-diethyl 2-methyl 2-iodocyclopropane-1,1,2-tricarboxylate.

We formerly established that in reaction of bicyclic or spirocyclic 2-pyrazolines with halogens (Cl_2, Br_2) formed esters of the corresponding 1-halocyclopropanecarboxylic acids built into 3-azabicyclo[3.1.0]-hexane or 5-azaspiro[2.4]heptane skeleton [1–3]. In the present study we investigated reactions of monocyclic 2-pyrazolines with halogens (Cl_2, Br_2) and iodinating agents (*N*-iodosuccinimide and a system iodine–silver trifluoroacetate). The initial 2-pyrazolines were prepared by treating esters of methylene and benzylidenemalonic acids with alkyl diazoacetates.

Methyl diazoacetate (**Ia**) reacted with ester **IIa** at room temperature, and ester **Ib** reacted with ester **IIb** at heating to 80°C, and thus pyrazolines **IIIa, b** were obtained in 57 and 34% yield respectively. The composition and structure of pyrazolines **IIIa, b** were established relaying on elemental analyses (Table 1) and spectral data (Table 2).



IIa, b **Ia, b** **IIIa, b**

I, R = Me (**a**), Et (**b**); **II**, R' = H (**a**), Ph (**b**); **III**, R = Me, R' = H (**a**); R = Et, R' = Ph (**b**).

In the ^{1}H NMR spectrum of pyrazoline **IIIa** is present a singlet from methylene protons of the pyrazoline ring at 3.54 ppm and a signal from NH proton at 7.13 ppm, and in the ^{1}H NMR spectrum of pyrazoline **IIIb** singlet of the methine proton appears at 5.63 ppm, and NH signal at 9.0 ppm.

In the IR spectra the absorption band corresponding to the stretching vibrations of N–H bond is observed at 3370–3390 cm^{-1}. In the ^{13}C NMR spectra the carbon atoms of pyrazoline ring appear as signals at 39.1 and 56.3 ppm for C^4 atoms of pyrazolines **IIIa, b** respectively. The signals of atoms C^3 are observed in the region 143–145 ppm, and those of C^5 atom at 76–81 ppm.

Reaction of pyrazolines **IIIa, b** with chlorine in dichloromethane gave rise to 1-pyrazolines **IVa, b** in 95% yield. In the ^{1}H NMR spectra the signals from methylene protons of compound **IVa** appear as doublets at 2.69 ppm (*J* 15 Hz) and 3.15 ppm (*J* 15 Hz), and the singlet of the methine proton from the pyrazoline **IVb** is observed at 4.62 ppm. In the ^{13}C NMR spectra the signals of carbon atoms from pyrazoline ring appear at 38.5 ppm for pyrazoline **IVa** and at 55.5 ppm for pyrazoline **IVb** (C^4), and also in the region 102–106 ppm (C^3, C^5).

The heating in a vacuum of pyrazoline **IVa** to 80°C and of pyrazoline **IVb** to 130°C resulted in formation of cyclopropanes **Va, b** in 95% yield. In the ^{1}H NMR spectrum of cyclopropane **Va** are seen the doublet signals from methylene protons of the three-membered ring at 2.20 ppm (*J* 7 Hz) and 2.40 ppm (*J* 7 Hz). The signals of carbon atoms of the three-membered ring of cyclopropane **Va** appear at 26.1 (C^3), 43.6 (C^1) and 46.2 (C^2) ppm.

Cyclopropane **Vb** formed as a mixture of *E* and *Z*-isomers in 4.7 : 1 ratio. In the ^{1}H NMR spectrum of compound **Vb** the methine singlet from cyclopropane ring of *E*-isomer appears at 3.89 ppm, that of *Z*-isomer at 3.84 ppm. In this spectrum are also observed

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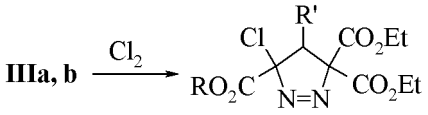
Table 1. Yields, melting points and elemental analyses of compounds synthesized

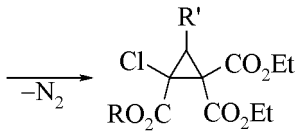
Compd. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa	57	–[a]	48.47	6.03	10.17	$C_{11}H_{16}N_2O_6$	48.53	5.92	10.29
IIIb	34	125–126[b]	59.69	6.03	7.59	$C_{18}H_{22}N_2O_6$	59.66	6.12	7.73
IVa	95	–[a]	43.88	5.12	8.89	$C_{11}H_{15}ClN_2O_6$	43.08	4.93	9.13
IVb	96	–[a]	54.39	5.36	6.89	$C_{18}H_{21}ClN_2O_6$	54.48	5.33	7.06
Va	95	–[a]	47.53	5.39	–	$C_{11}H_{15}ClO_6$	47.41	5.42	–
Vb	96	–[a]	58.57	5.81	–	$C_{18}H_{21}ClO_6$	58.62	5.74	–
VIa	16	80–81	48.57	4.99	14.01	$C_8H_{10}N_2O_4$	48.49	5.09	14.14
VIb	27	88–89	62.43	5.44	9.58	$C_{15}H_{16}N_2O_4$	62.49	5.59	9.72
VII	15	–[a]	49.05	4.63	6.17	$C_{18}H_{21}BrN_2O_6$	48.99	4.80	6.35
VIII	90	–[a]	52.29	5.04	–	$C_{18}H_{21}BrO_6$	52.32	5.12	–
IX	54	–[a]	35.54	4.17	–	$C_{11}H_{15}IO_6$	35.70	4.08	–

[a] Oily substance. [b] With decomposition.

signals from the aromatic protons and those of ester groups. In the ^{13}C NMR spectrum the carbon signals from the cyclopropane ring appear at 43.0 (C^3), 47.5 (C^1) and 49.3 (C^2) ppm for *E*-isomer and at 38.1 (C^3), 45.4 (C^1) and 51.5 (C^2) ppm for *Z*-isomer. Carbonyl carbons of *E*-isomer give rise to signals at 164.4, 164.6, and 165.1 ppm, those of *Z* at 163.2, 166.3, and 166.1 ppm. The signals of carbon atoms from OCH_2CH_3 group in *E*-isomer are located at 62.5, 62.8, and 63.4 ppm whereas those of *Z*-isomer appear at 62.9, 63.5, and 63.6 ppm. The configuration of isomeric cyclopropanes **Va, b** was assigned relying on upfield shift as compared to *E*-isomer of carbon signals from C=O and OCH_2CH_3 in the *Z*-isomer which is due to shielding of the ester group by a phenyl located *cis* to it. In *E*-isomer the ester group and phenyl are in *trans*-position [4].



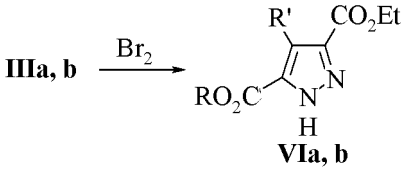
IVa, b



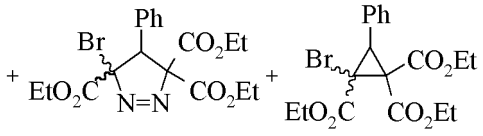
Va, b

IV, V, R = Me, R' = H (**a**), R = Et, R' = Ph (**b**).

The reaction of pyrazolines **IIIa, b** with bromine in dichloromethane at room temperature gave rise to complex mixtures that were subjected to column chromatography to isolate pyrazoles **VIa, b**, 1-pyrazoline **VII**, and cyclopropane **VIII** in 16, 20, 15, and 3% respectively. The ^1H NMR spectrum of pyrazoline **VII** shows that the compound contains *E*- and *Z*-isomers in 1 : 2.2 ratio. The signal of methine proton at C^4 appears at 4.65 in the spectrum of *Z*-isomer and at 4.73 ppm in that of *E*-isomer.



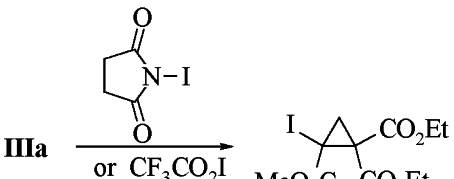
VIa, b



VIIa, b **VIII**

VI, R = Me, R' = H (**a**), R = Et, R' = Ph (**b**).

At heating pyrazoline **VII** in a vacuum at 110°C in 90% yield formed bromocyclopropane **VIII** also as



IX

Table 2. IR, ^{1}H and ^{13}C NMR spectra of compounds synthesized

Compd. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	^{13}C NMR spectrum, δ, ppm (*J*, Hz)
IIIa	870, 900, 1020, 1070, 1140, 1270 s, 1370, 1410, 1450, 1590, 1740 v.s, 3040, 3370	1.25 t (6H, 7), 3.54 s (2H), 3.80 s (3H), 4.22 q (4H, 7), 7.13 s (1H)	14.3, 39.1, 52.7, 63.3, 75.6, 142.7, 162.2, 168.3
IIIb	880, 1040, 1100, 1120, 1280, 1380, 1410, 1580, 1740 v.s, 3020, 3390	1.24 t (3H, 7), 1.56 t (3H, 7), 1.72 t (3H, 7), 4.11 m (2H), 4.52 m (2H), 4.72 m (2H), 5.63 s (1H), 7.59–7.79 (5H), 8.99 s (1H)	13.7, 14.3, 56.3, 61.6, 62.7, 63.4, 80.9, 128.5, 128.9, 129.0, 135.3, 145.0, 161.3, 166.6, 167.9
IVa	1020, 1100, 1140, 1270 s, 1370, 1450, 1600, 1730 v.s, 3050	1.32 m (6H), 2.69 d (1H, 14), 3.15 d (1H, 14), 3.89 s (3H), 4.33 m (4H)	14.3, 38.5, 54.8, 63.9, 102.9, 104.0, 164.7, 164.9, 165.5
IVb	880, 970, 1030, 1070, 1130, 1280 s, 1370, 1470, 1750 v.s., 2990	0.81 t (3H, 7), 0.87 t (3H, 7), 1.34 t (3H, 7), 3.83 q (2H, 7), 3.90 q (2H, 7), 4.35 m (2H), 4.62 s (1H), 6.88 m (2H), 7.25 m (3H)	13.6, 14.3, 55.5, 63.0, 63.2, 64.3, 102.1, 106.3, 128.9, 129.2, 129.3, 133.4, 163.4, 163.6, 164.1
Va	870, 980, 1020, 1090, 1140, 1270 s, 1380, 1440, 1740 v.s, 2990	1.26 t (3H, 7), 1.31 t (3H, 7), 2.20 d (1H, 7), 2.40 d (1H, 7), 3.81 s (3H), 4.18 q (2H, 7), 4.27 m (2H)	14.3, 14.4, 26.1, 43.6, 46.2, 54.1, 62.8, 63.2, 164.4, 165.6, 166.8
***E*-Vb**	[a] 870, 1040, 1130, 1270 s, 1370, 1450, 1730 v.s, 2990	1.10 t (3H, 7), 1.19 t (3H, 7), 1.37 t (3H, 7), 3.89 s (1H), 4.11 m (4H), 4.38 m (2H), 7.26–7.40 (5H)	13.9, 14.2, 14.5, 43.0, 47.5, 49.3, 62.5, 62.8, 63.4, 127.9, 128.2, 129.8, 131.4, 164.4, 164.6, 165.2
***Z*-Vb**		1.10 t (3H, 7), 1.19 t (3H, 7), 1.32 t (3H, 7), 3.84 s (1H), 4.18 m (4H), 4.32 m (2H), 7.26–7.40 (5H)	14.0, 14.2, 14.4, 38.1, 45.4, 51.5, 62.9, 63.5, 63.6, 129.1, 129.8, 130.2, 131.1, 163.2, 166.3, 166.4
VIa	950, 1020, 1090, 1170, 1270 s, 1330, 1450, 1570, 1730 v.s, 3050, 3420	1.38 t (3H, 7), 3.94 s (3H), 4.40 q (2H, 7), 7.33 s (1H), 10.5 s (1H)	14.5, 52.8, 62.1, 111.7, 140.1, 140.6, 160.6, 161.3
VIb	1020, 1100, 1180, 1390, 1450, 1610, 1720 v.s, 3050, 3420	1.20 t (6H, 7), 4.23 q (4H, 7), 7.35 m (5H), 13.0 br.s (1H)	14.2, 61.7, 127.6, 128.2, 128.3, 130.7, 131.0, 132.5, 137.6, 160.8
***Z*-VII**	[a] 870, 970, 1020, 1070, 1120, 1290 s, 1380, 1470, 1740 v.s, 2990	0.83 t (3H, 7), 1.31 t (3H, 7), 1.37 t (3H, 7), 3.87 q (2H, 7), 4.32 m (4H), 4.65 s (1H), 7.21–7.32 (5H)	13.9, 14.2, 52.1, 63.0, 64.1, 64.2, 99.8, 106.7, 128.8, 129.1, 129.5, 133.6, 162.7, 164.9, 165.1
***E*-VII**		0.82 t (3H, 7), 1.37 m (6H), 3.82 q (2H, 7), 4.26 m (4H), 4.73 s (1H), 7.21–7.32 (5H)	13.7, 14.4, 55.3, 62.8, 63.1, 64.5, 101.9, 105.8, 128.7, 129.1, 129.4, 133.4, 163.2, 163.3, 164.4
***Z*-VIII**	[a] 870, 1040, 1100, 1270 s, 1370 s 1450, 1730 v.s, 2990 s	1.22 t (3H, 7), 1.35 t (6H, 7), 3.70 s (1H), 4.28 m (6H), 7.28–7.44 (5H)	13.6, 14.3, 14.8, 39.1, 45.9, 51.4, 62.7, 63.7, 63.9, 126.9, 127.7, 128.9, 130.1, 163.4, 166.1, 166.3
***E*-VIII**		1.13 t (3H, 7), 1.36 t (6H, 7), 3.85 s (1H), 4.12 m (4H), 4.41 m (2H), 7.28–7.44 (5H)	13.7, 14.5, 14.7, 43.2, 47.4, 49.6, 62.6, 62.9, 63.8, 127.4, 127.9, 129.5, 131.2, 164.1, 164.3, 165.0
IX	970, 1020, 1090, 1270 s, 1350, 1380, 1450, 1730 v.s, 3050	1.21 t (3H, 7), 1.31 t (3H, 7), 1.89 d (1H, 7), 2.30 d (1H, 7), 3.72 s (3H), 4.13 m (2H), 4.28 m (2H)	2.7, 14.3, 14.6, 28.4, 41.7, 54.0, 62.8, 63.1, 165.5, 165.9, 167.9

[a] Mixture of *E*- and *Z*-isomers.

a mixture of *E*- and *Z*-isomers. In the ^{1}H NMR spectrum of cyclopropane **VIII** signals of the methine proton of the cyclopropane ring are observed at 3.70 ppm for *Z*-isomer and at 3.85 ppm for *E*-isomer.

The reaction of pyrazoline **IIIa** with *N*-iodosuccinimide or CF_3CO_2I (from iodine and CF_3CO_2Ag) gave rise to iodocyclopropane **IX** in 50% yield.

In the ^{1}H NMR spectrum of ester **IX** appear the methylene protons of cyclopropane ring as doublets at 1.89 and 2.30 ppm (*J* 7 Hz), and also signals from the protons of ester groups. In the ^{13}C NMR spectrum the carbon atoms of the cyclopropane ring are observed at 2.7 (C^2), 28.4 (C^3) and 41.7 (C^1) ppm. We failed to synthesize iodocyclopropane in reaction of ester **IIIb** with N-iodosuccinimide: 65% of the initial pyrazolone was obtained alongside a mixture of intractable products.

EXPERIMENTAL

IR spectra were recorded on spectrophotometer UR-20 from 2% solutions of compounds in chloroform. ^{1}H and ^{13}C NMR spectra were registered on spectrometer Bruker DPX-300 at operating frequencies 300.13 and 75.47 MHz respectively. The purity of substances was checked and reaction mixtures were analyzed by TLC on Silufol UV-254 plates.

5,5-Diethyl 3-methyl 4,5-dihydro-1*H*-pyrazole-3,5,5-tricarboxylate (IIIa). To a solution of 2 g (11.6 mmol) of ester **IIa** in 20 ml of ethyl ether was added 1 g (10 mmol) of ester **Ia**, the mixture was kept for 1 h at room temperature. The solvent was evaporated, the residue was purified by column chromatography on silica gel (eluent hexane–ethyl acetate, 1.8 : 1). On evaporation of the eluent 1.8 g of oily substance **IIIa** was obtained.

Triethyl 4,5-dihydro-4-phenyl-3*H*-pyrazole-3,5,5-tricarboxylate (IIIb). To a solution of 2 g (8 mmol) of ester **IIb** in 20 ml of benzene was added 2 g (17,5 mmol) of ester **Ib**. The mixture was heated to 80°C for 8 h. The benzene was distilled off, and hexane was added to the residue for crystallization. The separated precipitate was filtered off and washed with hexane. Yield 1 g.

5,5-Diethyl 3-methyl 4,5-dihydro-5-chloro-1*H*-pyrazole-3,5,5-tricarboxylate (IVa). Through a solution of 0.9 g (3.3 mmol) of pyrazoline **IIIa** in 10 ml of dichloromethane at room temperature was passed a flow of chlorine till the initial pyrazoline was totally consumed (TLC monitoring). The solvent was evaporated at room temperature. Yield 0.96 g.

Triethyl 4,5-dihydro-4-phenyl-5-chloro-3*H*-pyrazole-3,5,5-tricarboxylate (IV) was obtained in a similar way from 1 g (2.8 mmol) of pyrazoline **IIIb**. Yield 1.05 g.

1,1-Diethyl 2-methyl 2-chlorocyclopropane-1,1,2-tricarboxylate (Va). Pyrazoline **IVa** (0.96 g, 3.1 mmol) was heated in a vacuum at 80°C to the end of nitrogen liberation (10 min). Yield 83 g.

Triethyl 2-chloro-3-phenylcyclopropane-1,1,2-tricarboxylate (Vb). Pyrazoline **IVb** (1.05 g, 2.6 mmol) was heated in a vacuum at 130°C to the end of nitrogen liberation (10 min). Yield 94 g.

Pyrazoline IIIa reaction with bromine. To a solution of 0.43 g (1.6 mmol) of pyrazoline **IIIa** in 5 ml of dichloromethane was added 0.3 ml of bromine, and the mixture was kept for 3 days at room temperature. Then the reaction mixture was washed with 5% solution of Na_2SO_3, and dried over $MgSO_4$. The solvent was evaporated, the reaction products were subjected to column chromatography on silica gel to isolate 0.048 g (16%) of ester **VIa**, 0.062 g (14%) of the initial pyrazoline **IIIa**, and 0.391 g of unidentified products.

Pyrazoline IIIb reaction with bromine. (a) The process was performed as described above for pyrazoline **IIIa** with 0.32 g (0.9 mmol) of pyrazoline **IIIb** and 0.21 ml of bromine in chloroform. We obtained 0.051 g (20%) of ester **VIb**, 0.058 g (15%) of ester **VII** and 0.011 g (3%) of ester **VIII**. (b) To a solution of 0.5 g (1.4 mmol) of pyrazoline **IIIb** in 5 ml of glacial acetic acid was added 0.3 ml of bromine, and the mixture was heated to 80°C for 2 h. The solvent was distilled off, the residue was dissolved in ether, washed with 5% solution of Na_2SO_3, and dried on $MgSO_4$. The ether was evaporated, and the residue was subjected to column chromatography on silica gel (eluent hexane–ethyl acetate, 1 : 1) Yield 0.11 g.

Triethyl 2-bromo-3-phenylcyclopropane-1,1,2-tricarboxylate (VIII). Pyrazoline **VII** (0.04 g, 0.1 mmol) was heated in a vacuum to 110°C till the end of nitrogen liberation (5 min). Yield 0.03 g.

1,1-Diethyl 2-methyl 2-iodo-1,2,2-cyclopropanetricarboxylate (IX). (a) To a solution of 0.41 g (1.5 mmol) of pyrazoline **IIIa** in 10 ml of glacial acetic acid was added 0.42 g (1.9 mmol) of *N*-iodosuccinimide. The mixture was heated for 1 h to 70°C. The solvent was distilled off in a vacuum, the residue was dissolved in ether, washed with 5% solution of Na_2SO_3, and dried on $MgSO_4$. The ether was evaporated, and the residue was subjected to column chromatography on silica gel (eluent hexane–ethyl acetate, 2 : 1) Yield 0.28 g. (b) To a stirred mixture

of 0.30 g (1.1 mmol) of pyrazoline **IIIa** and 0.82 g (3.3 mmol) of silver trifluoroacetate in 8 ml of 1,2-dichloroethane heated to 70°C was added a solution of 0.42 g (1.6 mmol) of iodine in 6 ml of 1,2-dichloroethane. The mixture was stirred for another 30 min, cooled, and the precipitated AgI was filtered off. The organic layer was washed with 5% solution of Na_2SO_3, and dried on $MgSO_4$. The solvent was distilled off, and the residue was subjected to column chromatography on silica gel (eluent hexane–ethyl acetate, 2 : 1 by volume) Yield 0.22 g (54%).

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