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SYNTHESIS OF gem-DICHLOROCYCLOPROPYLMETHYLMALONATES AND DECARBOXYLATION

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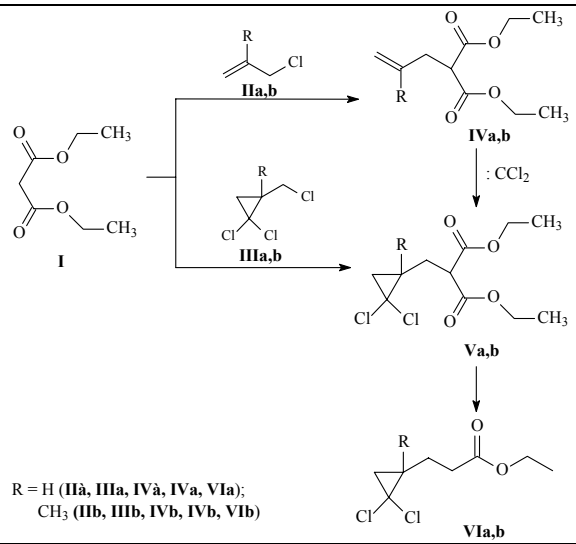
By studying the reaction of chloromethyl-gem-dichlorocyclic propanes and diethyl malonate the esters of acids including the cyclopropane fragments have been obtained. Their counter synthesis was carried out by carbonation of corresponding alkenyl malonates. By decarboxylation of substituted malonates the derivatives of cyclic propane carboxylic acids were synthesized. Efficiency of using the obtained products as plant growth regulators was proved.



INTRODUCTION

Polyfunctional cyclopropanes, particularly cyclopropane carboxylic acids and their derivatives are of great interest for the synthesis of biologically active compounds.[1,2] Bromomethyl-gem-dichlorocyclopropanes were previously used for addition of the cyclopropane group into the molecule of diethyl.[3] Chloromethyl-gem-dichlorocyclopropanes, formed during dichlorocarbenation of industrial available allyl chlorides, are more available reagents[4] than bromomethyl derivatives. So it is of interest to use chloromethyl-gem-dichlorocyclopropanes in alkylation process of *CH*-acids.

RESULTS AND DISCUSSION

It was established that in condition of phase transfer catalysis 2-chloromethyl-gem-dichlorocyclopropanes **IIIa,b** react with diethyl malonate **I** resulting in the formation of the adducts **Va,b** with yields (30-40%).

The alternative variant of *gem*-dichlorocyclopropylmethylmalonates, **Va,b** synthesis by the dichlorcarbenation of allylmalonates **IVa,b** allows to get/obtain the target products with yield of over 75%. The starting compounds **IVa,b** according to the well-known method,[5] *C*-alkylation of diethyl malonate **I** with chloroalkenes **IIa,b**.

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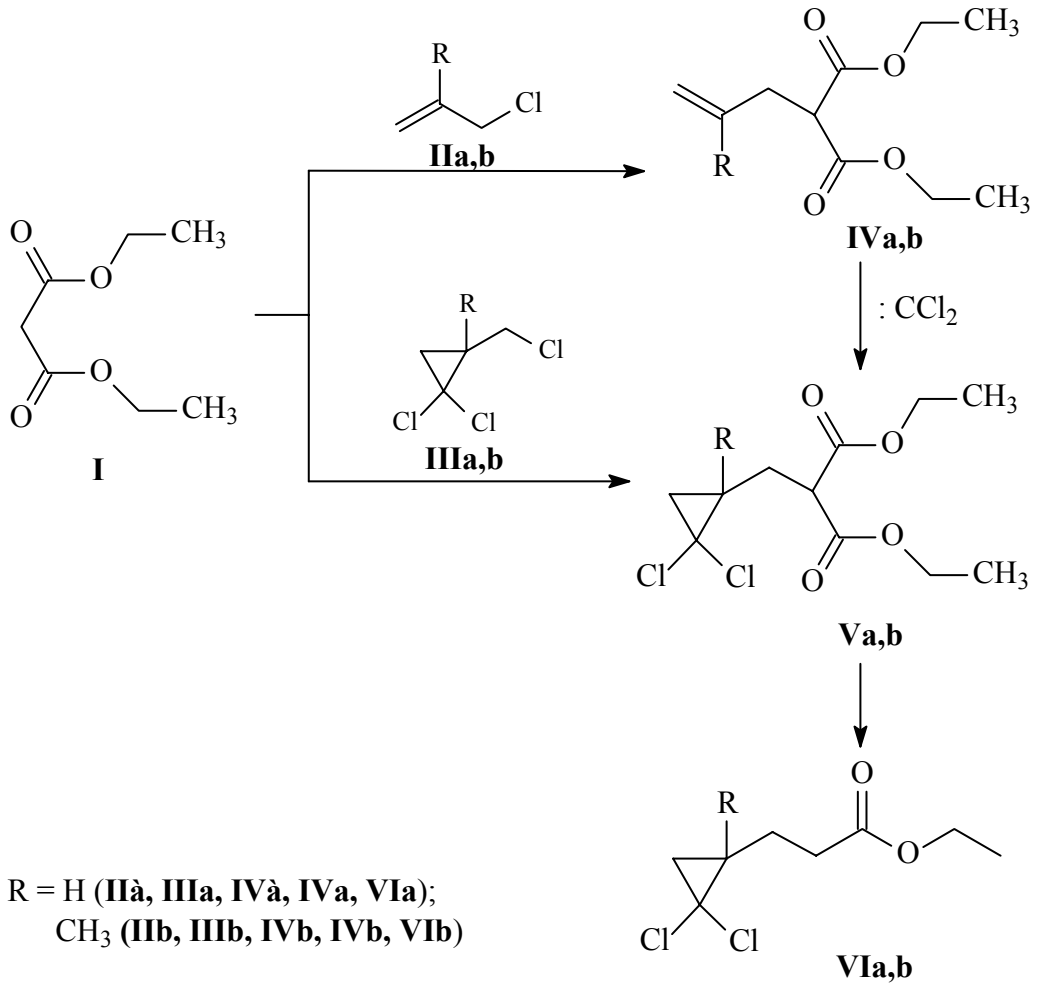
Considering the fact that the second method (of obtaining **Va,b**) gives the yield of over 75% and it is more effective/productive even though it consists of 2 stages.

Comparing the obtained results of our work with the results of the work[3] it appears that bromomethylcyclopropanes react with diester **I** more actively their than chlorine-containing analogues. It should be pointed out that in the reactions of *O*- and *N*-alkylation[1,6] there are not so many differences between the reaction capacity of bromomethyl and chloromethyl derivatives.

We obtained chlorvinyl derivative of malonic ester **I** based on the commercially available 1,3-dichloropropene **VII** in conditions of phase transfer catalysis in the presence of K_2CO_3 (yield of the product is 70%).

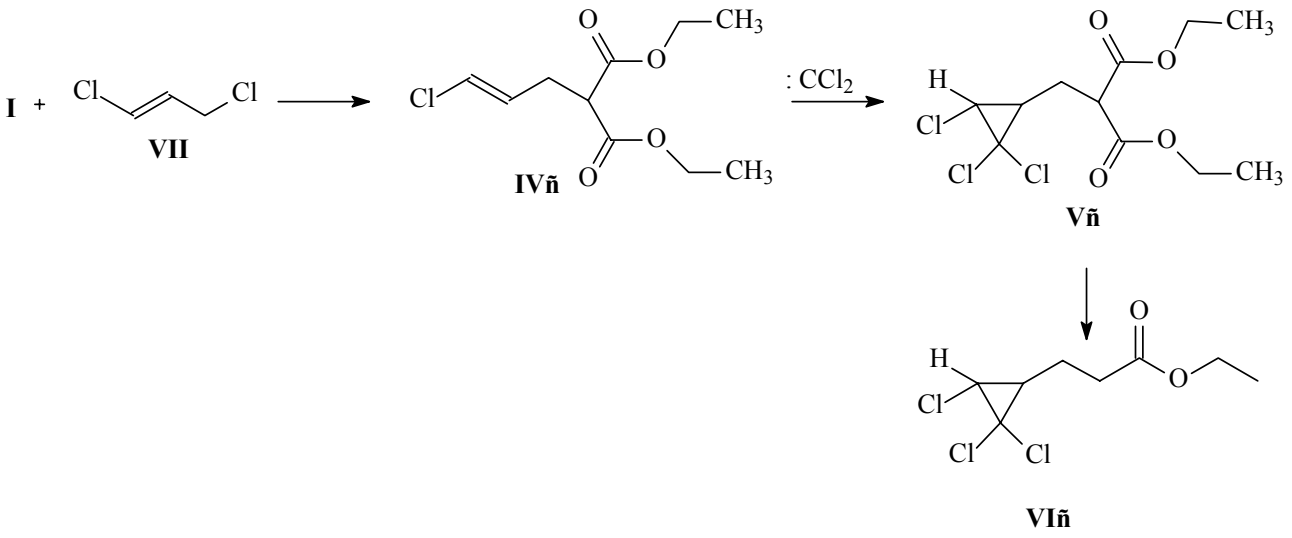


R = H (**IIà, IIIa, IVà, IVa, VIa**);
CH_3 **(IIb, IIIb, IVb, IVb, VIb)**

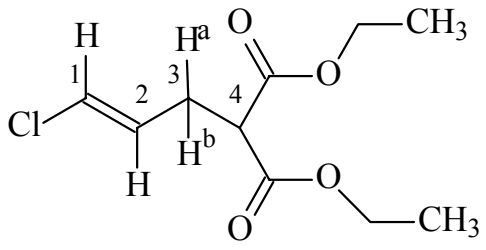
Table 1
Synthesis of substituted malonic esters

Reagents		*T*, ^{0}C	Reaction time, *h*	Products	Yield, %
I	**IIa**	50*	7	**IVa**	87
	IIb			**IVb**	82
	IIIa	80*	16	**Va**	35
	IIIb			**Vb**	30
IVa	$CHCl_3$	50**	7	**Va**	86
IVb				**Vb**	75

***** 0.06 M (II); 0.13 M (Va) or (Vb), or (Ia), or (Ib); 35 mL acetonitrile; 0.006 M TEBAC; 26 g K_2CO_3.
****** 0.1 M (IVa) or (IVb); 2.5 M of chloroform; 0.004 M TEBAC; 200 g 50% w/w solution of NaOH.



The structure of diethyl [(2E) -3-chloroprop-2-en-1-yl] malonate **IVc** is established on the basis of the result of ^{1}H NMR and mass-spectrometry.



***trans*-IVc**

In the ^{1}H NMR spectrum of the compound ***trans*-IVc** a proton H^1 at the first carbon atom resonates in 6.07 ppm as a doublet with a constant spin-spin interaction (SSCC) ^3J = 13.2 Hz, and in the compound ***cis*-IVc** it corresponds to doublet − 6.13 ppm with constant ^3J = 7.3 Hz, which in our case has not been detected. The values of constants of spin-spin interaction of H^1 and H^2 which equal to13.2 and 7.3 Hz respectively, according to the literature,[7,8] indicate to the *trans*- and *cis*-arrangement of protons H^1 and H^2, accordingly.

Protons H^1 and H^2 of the compound ***trans*-IVc** are in more weak field than would be observed in the isomer ***cis*-IVb** due to the influence of the substituents at carbon atoms C^1 and C^2. This is due to the fact that the signals of the olefinic protons are located in the weaker field to an electronegative substituent in the *cis*-position than in the *trans*-position.

Signals of the equivalent protons H^{3a} and H^{3b} in the compound ***trans*-IVc** are in a stronger field in comparison with isomer ***cis*-IVc**, which in our case was not observed. This is explained by the effect of an electronegative substituent – chlorine atom located at the carbon atom in the C^1-*trans* configuration to C^3H_2.

By NMR spectroscopy it was proven that stereoisomerism of the ***trans*-IVc** is saved after carbonation process and for carbene $:CCl_2$ it is typical attachment to the double bond of the alkene.

The possibility of preparing of biologically active compounds[9] by decarboxylation of malonates **Va-c** in DMSO at T = 140° C in the presence of lithium chloride (yield of the desired product **VIa-c** 70-80%) was investigated.

We studied the herbicidal activity of some synthesized compounds **IVa-c**. Primary biological studies of growth-regulatory activity were carried out in a laboratory on wheat and pea seedlings according to known method.[10]

The effectiveness of test compounds (Table 2) was determined in three days at T=25^{0}C compared to control (without chemicals) and the standard «Oktapon-Extra». The obtained data indicate that the preparation **IVb** exceeds the standard in inhibiting of shoot weight of peas.

The preparation **IVa** showed the best result on wheat comparable to the standard.

Table 2
Herbicidal activity of compounds **IVa-c**

Preparation	Concentration of AS, mg/L	Shoot length, mm	Inhibition, %	Shoot weight, g	Inhibition, %	Concentration of AS, mg/L	Shoot length, mm	Inhibition %	Shoot weight, g	Inhibition, %
	Pea						Wheat			
IVa	5	33	21	0.52	10.3	50	67	45	0.13	35
IVb	5	33	21	0.50	13.8	50	96	21	0.17	15
IVc	5	40	3	0.57	1.7	50	93	23	0.20	0
Standard	5	15	63	0.51	12.1	50	35	71	0.12	40
Control		42	—	0.58	—		—	122	—	0.20

* for dicotyledonous (pea) and monocotyledonous (wheat) plants – concentration of active substance (AS) 5 mg/L and 50 mg/L, accordingly.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.47 MHz respectively) solvent $CDCl_3$, internal standard Me_4Si. An Chrom-5 chromatograph was used for the qualitative and quantitative analysis of starting material and reaction products. The chromatograph was equipped with a thermo-conductivity detector (column is 1200-5 mm with 5% SE-30 on an Inerton N-AW DMCS (0.125–0.160 mm), a carrier gas – helium. Mass-spectra were recorded on a Thermo Finnigan MAT 95 XP (EI, 70 eV, ionization cell temperature 250°C, injector temperature 50–250°C, with a velocity of the temperature rise 10°C/min) and MX-1300 with insertion *via* a temperature balloon at 100°C with ionization energy of 12 and 70eV.

Initial alkyl malonates **IVa-c** have been prepared by *C*-alkylation of diethyl malonate with appropriate chloroalkenes according to the known method.[5]

General procedure of C-alkylation of diethyl malonate (**I**): a mixture of 0.06 M of diethyl malonate **I**, 0.13 M chloroderivation **IIa**,**b** (or **IIIa,b**, or 1,3-dichloropropene **VII**), 35 mL of acetonitrile, 0.006 M of a phase transfer catalyst TEBAC (triethyl benzyl ammonium chloride) or dibenzo-18-crown-6 (in case of **VII**) and 0.26 M K_2CO_3 was stirred at 40°C for 7 h [in case of **IIIa,b** at 80^{0}C, 16h; or in case of **VII** at 60°C for 7h]. The mixture was cooled down to rt, washed with water and extracted with hexane. Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

Diethyl-2-allylmalonate **(IVa)**: b.p. 85^{0}C (5 mm Hg). ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 0.85 m (6H, C^5H_3, C^7H_3), 2.60 m (2H, C^8H_a, C^8H_b), 3.30 m (1H, C^2H), 3.90 m (4H , C^4H_a, C^4H_b, C^6H_a, C^6H_b), 4.89 d (1H, $C^{10}H_a$, ^2J 1.6, ^3J 17.1), 5.00 dd (1H, $C^{10}H_b$, ^3J 10.2), 5.71 m (1H, C^9H). NMR ^{13}C ($CDCl_3$, δ, ppm): 13.9 (C^5H_3, C^7H_3), 32.2 (C^8H_2), 51.3 (C^2H), 61.1 (C^4H_2, C^6H_2), 116.4 ($C^{10}H_2$), 138.0 (C^9H), 168.3 (C^1=O, C^3=O). Mass spectrum *m/e*, (I,%): 200 (3), 160 (2), 155 (10), 127 (72), 109 (100), 98 (78), 29 (18).

Diethyl-2-(2-methylprop-2-en-1-yl)malonate **(IVb)**: b.p. 89^{0}C (5 mm Hg). ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 0.89 m (6H, C^5H_3, C^7H_3), 1.50 c (3H, $C^{11}H_3$), 2.70 d (2H, C^8H_a, C^8H_b, ^3J 7.6), 3.60 m (1H, C^2H), 3.88 m (4H, C^4H_a, C^4H_b, C^6H_a, C^6H_b), 4.74 d (2H, $C^{10}H_a$, $C^{10}H_b$, ^3J 19.5). NMR ^{13}C ($CDCl_3$, δ, ppm): 14.4 (C^5H_3,C^7H_3), 22.6 ($C^{11}H_3$), 37.2 (C^8H_2), 51.2 (C^2H), 61.5 (C^4H_2, C^6H_2), 112.8 ($C^{10}H_2$), 142.6 (C^9H), 169.3 (C^1=O, C^3=O). Mass spectrum *m/e*, (I, %): 214 (<1) $[M]^{\bullet+}$, 169 (13), 141 (100), 123 (61), 112 (34), 95 (82), 55 (15), 41 (10).

Diethyl[(2,2-dihlorocyclopropyl)methyl]malonate **(Va)**: b.p. 170^{0}C (5 mm Hg). The obtained physico-chemical constants, NMR and mass spectra correspond to the literature data.[6]

Diethyl[(2,2-dichloro-1-methylcyclopropyl)methyl]malonate **(Vb)**: b.p. 190^{0}C (5 mm Hg). The obtained physico-chemical constants, NMR and mass spectra were consistent with the literature data.[6]

Diethyl-2-[(2E)-3-chloroprop-2-enyl]malonate (**IVc**): b.p. 110°C (5 mm Hg). ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz) :). 0.90 s (6H, C^5H_3, C^7H_3), 2.80 m (2H C^1H_2), 3.30 m (1H, C^2H_1), 4.00 m (4H, C^4H_2, C^6H_2), 6.07 d (2H, $C^{2'}H_1$ $C^{3'}H_1$ ^3J 13.2). NMR ^{13}C ($CDCl_3$, δ, ppm): 13.9 (C^6H_3, C^7H_3), 26.7 ($C^{10}H_2$), 51.4 (C^2H), 61.3 (C^4H_2, C^5H_2), 120.6 (C^8H_2, C^9H_2), 172.2 (C^1=O,C^3=O). Mass spectrum *m/e*, (I, %): 243 (12) $[M]^{\bullet+}$, 199/30, 160/32, 125/100/97/62, 75/20, 53/10.

General procedure of carbenation of diethyl-2-allylmalonate (IVa), diethyl-2-(2-methylprop-2-en-1-yl)malonate (IVb) and diethyl[(2E)-3-chloroprop-2-en-1-yl]malonate (IVc): to the mixture of 0.1 M allylmalonate **IVa-c**, 2.5 M chloroform, 0.004 M phase transfer catalyst (TEBAC) with vigorous stirring and heating till 50°C, 200 g of 50% NaOH solution was added for 1 h. Then the reaction mass was stirred at 50°C for 7 h. The mixture was cooled down to rt, washed with water. Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

Diethyl[(2,2-dihlorocyclopropyl)methyl]malonate **(Va)**: b.p. 170^{0}C (5 mm Hg). The obtained physico-chemical constants, NMR and mass spectra correspond to the literature data.[6]

Diethyl[(2,2-dichloro-1-methylcyclopropyl)methyl]malonate **(Vb)**: b.p. 190^{0}C (5 mm Hg). The obtained physico-chemical constants, NMR and mass spectra were consistent with the literature data.[6]

Diethyl[(2,2,3-trichlorocyclopropyl)methyl]malonate (**Vc**): b.p. 160°C (2 mm Hg). ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 1.32 s (6H, C^6H_3, C^7H_3), 2.15 m (1H C^9H), 2.33-2.55 m (2H, $C^{11}H_a$, $C^{11}H_в$), 3.75 m (1H, C^8H), 3.80 m (1H, C^2H), 4.25 m (4H, C^2H_2, C^4H_2). NMR ^{13}C ($CDCl_3$, δ, ppm): 14.1 (C^6H_3, C^7H_3), 24.7 ($C^{11}H_2$), 36.4 (C^9H), 41.3 (C^8H), 51.3 (C^2H), 59.6 (C^{10}), 61.3 (C^4H_2, C^5H_2), 168.2 (C^1=O, C^3=O). Mass spectrum *m/e*, (I, %): 315/317 $M^{+\cdot}$ (No), 231/233 (42/13), 187/189 (100/35) 157/159/161 (12/4/2), 143/145 (10/3), 99/101 (11 / 3), 75 (9).

General procedure of decarboxylation of cyclopropyl malonates Va-c: 0.01 M diethyl-2-[(2,2-dichlorocyclopropyl)methyl]malonate (Va) (or diethyl-2-[(2,2-dichloro-1-methylcyclopropyl)methyl]malonate (Vb), or diethyl-2-[(2,2,3-trichlorocyclopropyl)methyl]malonate (Vc)) 0.03 M lithium chloride, 0.03 M of water and 15 mL of DMSO. The mixture was stirred and heated at 140°C for 7 h to complete conversion of the substrate. The mixture was cooled down to rt, washed with water and extracted with chloroform. Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

Ethyl-3-(2,2-dichlorocyclopropyl)propanoate (**Vl a**): b.p. 111°C (9 mm Hg). ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 1.15 m (1H, C^5H_1), 1.30 s (3H, C^1H_3), 1.60 m (C^6H_a, C^6H_b, ^2J 7.2) 1.85 m (2H, C^4H_a, C^4H_b, ^2J 7.2) 2.50 m (2H, C^3H_a, C^3H_b), 4.00 m (2 H, C^2H_2, ^2J 7.1). NMR ^{13}C ($CDCl_3$, δ, ppm): 14.2 (C^1H_3,), 25.8 (C^5H_2), 26.7 (C^4H_2), 33.0 (C^6H_2), 60.5 (C^2H_2), 61.0 (C^8), 172.2 (C^3=O). Mass spectrum *m/e*, (I, %): 211 (<1) $[M]^{\bullet+}$, (164/166/168) / (54/23/10), (136/138/140) / (23 / 10/6) (122/124/126) / (60/23/16), (111/113/115) / (41/20/7), 101/95 (88/90/92) / (100/21/5), 60/65.

Ethyl-3-(2,2-dichloro-1-methylcyclopropyl)propanoate (**Vl b**): b.p. 120°C (9 mm Hg). ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 1.10 (3H, C^1H_3), 1.30 s (3H, C^6H_3), 1.95 m (2H, C^5H_a, C^5H_b), 2.10m (2H, C^4H_a, C^4H_b, ^2J 6.1, ^3J 10), 2.50 m (2H, C^3H_a, C^3H_b, ^3J 9.9), 4.10 m (2H, C^2H_a, C^2H_b,). NMR ^{13}C ($CDCl_3$, δ, ppm): 14.2 (C^1H_3), 19.5 (C^8H_3), 29.4 (C^9H_2), 30.4 (C^4H_2), 31.9 (C^6H_2), 35.1 (C^5), 60.5 (C^2H_2), 65.5 (C^7), 172.6 (C^3=O). Mass spectrum *m/e*, (I, %): 225 (<1) $[[M]^{\bullet+}$, (189/191/193) / (36/13/5), 153/23, (141/143/145) / (55/21/5), 125/21, (115/117/119) / (60/24/3), (99/101/103) / (40/15/2), 88/100, 79/41, 70/35.

Ethyl-3-(2,2,3-trichlorocyclopropyl)propanoate (**Vl c**): b.p. 130°C (4 mm Hg). ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 1.30 (3H, C^1H_3), 1.75 m (1H, C^5H), 1.85 m (1H, C^4H_a), 1.95 m (1H, C^4H_b), 2.40 m (1H, C^3H_a), 2.50 m (1H, C^3H_b), 3.20 m (1H, C^6H), 4.75 m (2H, C^6H_a, C^6H_b, ^2J 5). NMR ^{13}C ($CDCl_3$, δ, ppm): 14.2 (C^1H_3,), 24.4 (C^5H_2), 32.3 (C^4H_2), 39.0 (C^6H), 45.0 (C^7H), 60.8 (C^2H_2), 63.4 (C^8), 172.2 (C^3=O). Mass spectrum *m/e*, (I, %): 245 (<1) $[M]^{\bullet+}$, (209/211/213) / (78/45/8), (181/183/185) / (40 / 15/3) (163/165/167) / (9/6/1), 145/36, (135/137/139) / (100/30/11) (99/101/103) / (31/9/4), 65/20 /

The procedure of biological studies

Petri dishes are incubated for 3 days at 24-25°C. The effectiveness of the test compounds (the degree of inhibition of growth and shoot mass) was determined in percent compared to control (without chemicals). Replication of tests − three times. We used as a standard the known herbicide «Oktapon-Extra», which is registered and included in the list of pesticides permitted for use in the Russian Federation.[11]

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