SYNTHESIS OF AROMATIC AND HETEROCYCLIC ANALOGS OF THE NATURAL GROWTH INHIBITOR ABSCISSIC ACID

N. D. Livshits, Ch. Sh. Kadyrov, and N. D. Abdullaev

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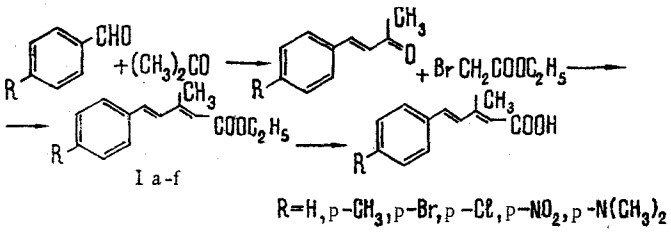
We have previously reported the synthesis of a natural inhibitor – abscissic acid – and a number of its analogs [1, 2]. In order to broaden this series and also to elucidate the sterochemistry of the products obtained we have synthesized penta-2,4-dienoic acids containing phenyl, furyl, and heterocyclic rings. The reaction was performed in two ways: by the Reformatsky condensation and by the Wittig method.

For aromatic aldehydes containing such substituents as H, CH_3, and Cl, the reaction was performed in benzene in the presence of activated zinc dust. The reaction took place fairly smoothly except for the case of p-chlorobenzylideneacetone – in this case only traces of product were obtained. The chlorine atom probably deactivated the organozinc compound obtained and the reaction did not proceed.



Scheme 1

It is known that the presence of a nitro group in a carbonyl compound prevents the Reformatsky reaction under the usual conditions [3]. We used a modified Reformatsky synthesis [4] for substituted benzylideneacetones containing Cl, $N(CH_3)_2$, and NO_2 groups. According to the results of GLC analysis (Table 1), regardless of the substituent, the trans, trans isomer predominated in the mixture of penta-2,4-dienoic acids obtained.

Since the various esters of penta-2,4-dienoic acids obtained as the result of the Reformatsky condensation each contained mainly the trans, trans isomer, for their synthesis we also used the Wittig method, by means of which the required cis, trans isomer was present in each mixture in predominating amount [2] (Table 2).

Some esters of substituted 5-phenylpenta-2,4-dienoic acids in the form of mixtures of isomers were separated into the individual isomers with the aid of preparative GC chromatography using as the stationary phase 5% of XE-60 deposited on Khrezosorb, 0.4-0.6 mesh, temperature 195°C, carrier gas nitrogen. The individualities of the separated isomers were checked by analytical GLC and also by PMR spectroscopy.

The series of analogs of abscissic acid containing a furan nucleus in the molecule has been broadened [2]. The condensation of furfurylideneacetones with carboxymethylenetriphenylphosphorane yielded, in the form of mixtures of two geometrical isomers in each case, esters of substituted furylpentadienoic acids with CH_3 and Br as substituents. Saponification of the latter gave the corresponding acids. The reactions were performed by fusing the reactants at 160-170°C. The yield of products was 63-72%. The esters formed were freed from by-products by plate chromatography.

In all the substituted furylpentadienoic esters (acids) the cis, trans isomer was predominant in the mixture, which can be explained by its stability because of the partial attraction by the electron pair of the oxygen of the positively charged carbon of the carboxyl. Where the substituent in the nucleus was bromine, the amount

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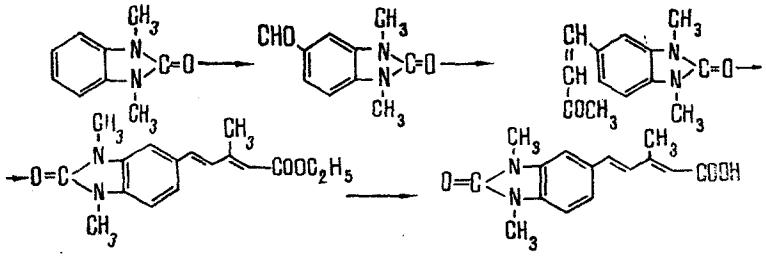
TABLE 1. Ethyl Esters of 5-Aryl-3-methylpenta 2,4-dienoic Acids

Compound	R	bp, °C (mm)	Yield, %	Ratio of the isomers in the mixture	
				cis, trans	trans, trans
Ia	H	142–150 (3)	55	45	55
Ib	p-CH_3	134–149 (3)	46	41	59
Ic	p-Cl	178–185 (2)	57	38	62
Id	p-Br	189–196 (3)	42	37	63
Ie	p-$N(CH_3)_2$	188–194 (2,5)	26	28	72
If	p-NO_2	190–198 (2)	22	—	—

Note. Stationary phase – 5% of XE-60 deposited on Chromaton N-AW-MDW, column length 2 m, diameter 4 mm, carrier gas nitrogen, rate of flow 30 ml/min, temperature 190°C.

of cis, trans isomer in the mixture fell somewhat in view of the fact that bromine, by drawing electrons to itself, lowers the total electron density of the nucleus and, consequently, the partial charge on the oxygen atom also decreases, which has an adverse influence on the stability of the cis, trans isomer. When the substituent in the nucleus was a methyl group, the ratio of the isomers changed in the direction of a greater predominance of the cis, trans isomer than in the case of bromine, which is probably due to its electron-donating nature (Table 3).

To synthesize structural analogs of abscissic acid including a nitrogen-containing nucleus we took 1,3-dimethylbenzimidizolin-2-one and 2-methylbenzimidazole

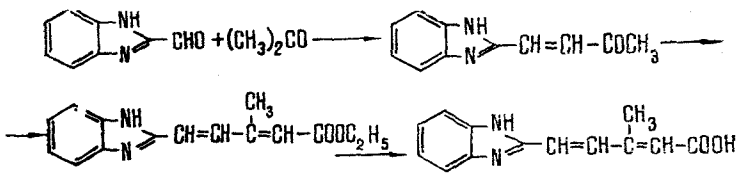


Scheme 2

The aldol condensation of 1,3-dimethylbenzimidizolin-2-one with acetone yielded 1,3-dimethyl-2-oxobenzimidazolin-5-ylvinyl methyl ketone. Its PMR spectra has a six-proton singlet at 3.37 ppm from two equivalent $=N-CH_3$ groups. The olefinic protons appear at 6.60 and 7.05 ppm in the form of doublets with J = 16 Hz, and there is a three-proton singlet of the ketone methyl group at 7.31 ppm.

Condensation of this ketone with ethoxycarbonylmethylenetriphenylphosphorane led to the corresponding pentadienoic ester, the saponification of which gave 5-(1,3-dimethyl-2-oxobenzimidazolin-5-yl)-3-methylpenta-2,4-dienoic acid in the form of a mixture of two isomers. The reaction was performed in the absence of a solvent, by fusion. The ester was separated from the by-products by extraction with hydrochloric acid and by preparative thin-layer chromatography. The structure of the compounds obtained was confirmed by PMR spectroscopy and also by elementary analysis.

Ethyl 5-(benzimidazol-2-yl)penta-2,4-dienoate and the corresponding acid were synthesized analogously.



Scheme 3

TABLE 2. Properties of the Compounds Obtained

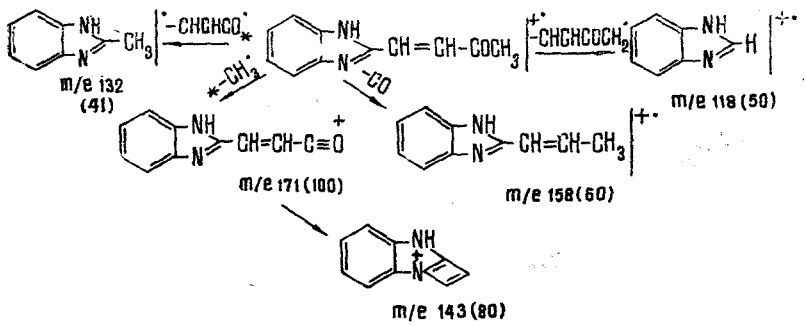
Compound	mp, °C (solvent). bp, °C (mm)	n_D^{20}	Yield, %	Residence time, min	Ratio of the isomers	
					cis, trans	trans, trans
1. Ethyl 3-methyl-5-phenylpenta-cis-2,trans-4-dienoate	-	1,6091	42	5	100	-
2. Ethyl 3-methyl-5-phenylpenta-trans-2,trans-4-dienoate	-	1,6079	48	6,5	-	100
3. Ethyl 5-(p-bromophenyl)-3-methylpenta-cis-2,trans-4-dienoate	42-43	-	40	19	100	-
4. Ethyl 5-(p-bromophenyl)-3-methylpenta-cis-2,trans-4-dienoate	84-85	-	44	25	-	100
5. Ethyl 5-(o-methoxyphenyl)-3-methylpenta-cis-2,trans-4-dienoate	-	1,5990	51	7,4	100	-
6. Ethyl 5-(o-methoxyphenyl)-3-methylpenta-trans-2, trans-4-dienoate	-	1,6008	28	8,9	-	100
7. Ethyl 3-methyl-5-(5'-methylfuryl)penta-2,4-dienoate	135-144 (2,5)	1,6123	67	11,3 12,8	58	42
8. 3-Methyl-5-(5'-methylfuryl)-penta-2,4-dienoic acid	166-168 (petroleum ether)	-	77	-	60	40
9. Ethyl 5-(5'-bromofuryl)-3-methylpenta-2,4-dienoate	163-172 (5)	1,6532	63	17 20,5	55	45
10. 5-(5'-Bromofuryl)-3-methylpenta-2,4-dienoic acid	224-226 dil. ethanol	-	76	-	-	-
11. Ethyl 5-(1,3-dimethyl-2-oxobenzimidazolin-5-yl)-3-methylpenta-2,4-dienoate	78	-	75	-	55	45
12. 5-(1,3-Dimethyl-2-oxobenzimidazolin-5-yl)-3-methylpenta-2,4-dienoic acid	204-205	-	80	-	55	45
13. Ethyl 5-(benzimidazol-2-yl)-3-methylpenta-2,4-dienoate	146-148 dil. ethanol	-	56	-	60	40
14. 5-(Benzimidazol-2-yl)-3-methylpenta-2,4-dienoic acid	97-98 reprecipitation	-	72	-	-	-

TABLE 3. Chemical Shifts of the Protons of the Side Chains of Compounds R—CH(5)=CH(4)—C(CH$_3$)(3)=CH(2)—COOC$_2$H$_5$(1)

Compound	C_5H		$C_3(CH_3)$		C_4H		C_2H		$COOCH_2CH_3$	
	cis, trans	trans, trans	cis, trans	trans, trans	cis, trans	trans, trans	cis, trans	trans, trans	CH_3	CH_2
1	5,60 s	—	2,07 s	—	8,35 d	—	6,76 d	—	1,23 t	4,09 q
2	—	5,76 s	—	2,32 s	—	6,63 d	—	6,83 d	1,22 t	4,07 q
3	5,62 s	—	2,03 s	—	8,34 d	—	6,67 d		1,24 t	4,07 q
4	—	5,77 s	—	2,31 s	—	6,62 s	—	6,79 s	1,23 t	4,1 q
5	5,57 s	—	2,06 s	—	8,30 d	—	6,61 d	—	1,22 t	4,07 q
6	—	5,73 s	—	2,34 s	—	—	—	—	1,23 t	4,06 q
7	5,52 s	5,71 s	1,95 s	2,26 s	8,07 d	6,1 d	6,46 d	6,15 s	1,23 t	4,07 q
8	5,56 s	5,77 s	2,08 s	2,27 s	7,97 d	—	—	—	—	—
9	5,58 s	5,77 s	1,99 s	2,26 s	8,13 d	—	—	—	1,25 t	4,09 q
10	5,62 s	5,80 s	2,06 s	2,26 s	8,11 d	—	—	—	—	—
11	5,56 s	5,74 s	2,06 s	2,31 s	8,28 d	6,7 d	—	6,9 d	1,26 t	4,1 q
12	5,42 s	5,55 s	1,84 s	2,05 s	7,91 d	6,6 d	—	6,9 d	—	—
13	5,47 s	5,52 s	1,82 s	2,072 s	—	—	—	—	1,15 t	4,0 q

Note: s) singlet; d) doublet; t) triplet; q) quartet.

The condensation of benzimidazole-2-carbaldehyde with acetone yielded benzimidazole-2-ylvinyl methyl ketone, the structure of which was confirmed by mass spectrometry. The fragmentation and the direction of breakdown of the molecular ion corresponded completely to the structure given below (the asterisks denote metastable transitions).



Scheme 4

The fusion of molar amounts of the ketone with ethoxycarbonylmethylenetriphenylphosphorane gave ethyl 5-(benzimidazolin-2-yl)penta-2,4-dienoate and, after saponification, the corresponding acid. The structures of the compounds obtained were confirmed by PMR and IR spectroscopy, and also by elementary analysis.

The IR spectrum of 5-(benzimidazolin-2-yl)-3-methylpenta-2,4-dienoic acid contained absorption bands at 1695 cm^{-1} (C=O group of an acid), 1620, 1600 cm^{-1} (conjugated system of double bands), 2856-3060 cm^{-1} (vibrations of the NH group of an imidazole ring), and also νCH of an aromatic ring.

The abscissic acid analogs synthesized were tested in separate biological tests in the form of the individual isomers. The tests were performed on wheat coleoptiles and on pea shoots with the aim of investigating growth-inhibiting activity. The introduction of a halogen into the aromatic ring considerably increased inhibition on wheat coleoptiles, the two isomers (cis, trans, and trans, trans) showing approximately the same activity at low concentrations – $2 \cdot 10^{-3}$ M (400 mg/liter). Nevertheless, there was no inhibition on pea shoots.

When a methoxy group was introduced into the aromatic ring of the molecule, again an increase in inhibition on wheat coleoptiles, and also on pea shoots was observed. In this case, the cis, trans isomer showed a greater activity than the trans;trans isomer. The tests were carried out at concentrations of 800 and 400 mg/liter (Table 4).

In spite of the fairly considerable inhibition on wheat coleoptiles and pea shoots, the aromatic analogs were 300-400 times weaker than abscissic acid itself. This fact emphasizes the specific nature of the structure of abscissic acid as an effective natural growth inhibitor.

TABLE 4. Growth-Inhibiting Activity of Abscissic Acid Analogs, % on Control

Compound	Inhibition on wheat coleoptiles				Inhibition on pea shoots							
	repititions of experiments											
	1	2	1	2	1	2	3	4	1	2	3	4
	800		400		800				400 mg/liter			
The ethyl ester of (II)*	0	0	14	18	0	0	0	0	4	5	12	18
The ethyl ester of (III)	0	0	28	26	0	0	0	0	21	26	16	18
The methyl ester of (III)	16	18	30	33	0	0	0	0	12	14	16	17
The ethyl ester of (IV)	20	22	53	58	31	31	34	35	45	50	42	42
The ethyl ester of (V)	23	24	49	49	5	5	5	5	33	35	37	40
The ethyl ester of (VI)	38	32	53	55	8	8	8	10	17	17	14	10
The ethyl ester of (VII)	28	35	59	60	0	0	0	0	0	0	0	0
o-Methoxybenzylidene acetone	0	0	0	0	0	0	0	0	0	0	0	0

At a concentration of abscissic acid of 1 mg/liter, inhibition on wheat coleoptiles was 33% and on pea shoots 89%.

* See experimental part.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer, the mass spectra on an MKh-1003 instrument, and the PMR spectra on a JNM-4H 100/100 MHz instrument with hexamethyldisiloxane as internal standard (δ scale).

The elementary analyses corresponded to the calculated figures.

Ethyl 5-(p-Bromophenyl)-3-methylpenta-2,4-dienoate. To 2.25 g (0.01 mole) of p-bromobenzylideneacetone in 15 ml of absolute benzene in a current of nitrogen was added 1.5 ml (0.012 mole) of ethyl bromoacetate. The mixture was heated to the boil, and 0.77 g (0.11 g-atom) of activated zinc was added in small portions. The mixture was boiled for 2 h and was then cooled and shaken with 50 ml of 5% H_2SO_4. The organic layer was separated off and the aqueous layer was extracted with benzene. The benzene extracts, combined with the organic layer, were washed and dried, and the solvent was distilled off. This gave 2.6 g of an oil. To this were added 30 ml of dry benzene and 0.9 g (0.0075 mole) of $NaHSO_4$ and the mixture was heated in the oil bath with the simultaneous distillation of water for 2 h. Then the mixture was diluted with water, washed, and extracted with ether. The extract was washed and dried and the solvent was distilled off. Yield 1.23 g (42%) of ethyl 5-(p-bromophenyl)-3-methylpenta-2,4-dienoate; yellow oil, R_f 0.780, 0.895 [petroleum ether–diethyl ether (2:1) system]. Compounds (Ia and b) were obtained similarly (see Table 1).

Ethyl 5-(p-Chlorophenyl)-3-methylpenta-2,4-dienoate. To a solution of the Reformatsky reagent obtained from 8 g of amalgamated zinc, 1 ml of CH_3MgI, and 10 g (0.06 mole) of ethyl bromoacetate in 100 ml of absolute ether, after decantation, was added 5.4 g (0.03 mole) of p-chlorobenzylideneacetone, and the mixture was boiled for 2 h and was then cooled. The contents of the flask were hydrolyzed with 10% CH_3COOH. The organic layer was separated off and the aqueous layer was extracted with ether. The ethereal layer, combined with the organic layer, was washed and dried. Dehydration of the product with 3.6 g (0.03 mole) of $NaHSO_4$ gave 4.27 g (57%) of ethyl 5-(p-chlorophenyl)-3-methylpenta-2,4-dienoate, R_f 0.73, 0.842.

Ethyl 5-(5'-methylfuryl)-3-methylpenta-2,4-dienoate. A mixture of 1.37 g (0.01 mole) of ethoxycarbonylmethylentriphenylphosphorane was fused in an oil bath in a current of nitrogen at 150-160°C for an hour. The cooled mass was treated with ether, the crystals that precipitated were separated off, the mother liquor was concentrated, and the residue was distilled in vacuum. Yield 1.4 g (67%) of 5-(5'-methylfuryl)-3-methylpenta-2,4-dienoic acid with bp 135-144°C (2.5 mm). Compound 9 was obtained similarly (see Table 2).

1,3-Dimethyl-2-oxobenzimidazolin-5-ylvinyl Methyl Ketone. To a solution of 2.46 g (0.013 mole) of 1,3-dimethylbenzimidazol-5(6)-carbaldehyde [5] in 10 ml of ethanol were added 7.5 ml (0.13 mole) of acetone and then, with stirring, 6 ml of 5% ethanolic NaOH solution and 4 ml of water. The reaction mixture was stirred for an hour at room temperature and was acidified with 5% HCl to pH 6; the crystals that deposited were filtered off. The addition of 20 ml of ether to the evaporated solution led to the appearance of more crystals. Yield 1.9 g (57%) of 1,3-dimethyl-2-oxobenzimidazolin-5-ylvinyl methyl ketone. White crystals, mp 168-169°C (decomp., ethanol), R_f 0.48 [ethyl acetate–ether (1:1) system].

Benzimidazol-2-ylvinyl Methyl Ketone. Under similar conditions, 2.19 g (0.025 mole) of benzimidazole-2-carbaldehyde [6] and 11 ml (0.25 mole) of acetone yielded 1.5 g (52%) of benzimidazol-2-ylvinyl methyl ketone. Yellow crystals, mp 165-167°C (aqueous ethanol), R_f 0.436 [ethyl acetate–ether–petroleum ether (5 : 11 : 6) system].

Ethyl 5-(1,3-Dimethyl-2-oxobenzimidazolin-5-yl)-3-methylpenta-2,4-dienoate. A mixture of 0.96 g (0.0044 mole) of 1,3-dimethyl-2-oxobenzimidazolin-5-ylvinyl methyl ketone and 1.74 g (0.005 mole) of ethoxycarbonylmethylenetriphenylphosphorane was heated in a current of nitrogen at 137-147°C for 1.5 h. The resulting soild mass, after cooling, was treated with ether in the cold. The crystals that deposited were filtered off and the mother liquor was extracted repeatedly with 5% HCl. After treatment with bicarbonate, 0.99 g (75%) of ethyl 5-(1,3-2-oxobenzimidazolin-5-yl)-3-methylpenta-2,4-dienoate was obtained in the form of white crystals with mp 78°C (decomp., ethanol), R_f 0.665, 0.73 [benzene–acetone (1 : 1) system].

Compound 13 was synthesized similarly.

After preparative separation of the esters and their saponification [7], the following acids were obtained:

II – 3-methyl-5-phenylpenta-cis-2,trans-4-dienoic acid, mp 157-158°C [8].
III – 3-methyl-5-phenylpenta-trans-2,trans-4-dienoic acid, mp 161-161.5°C [8].
IV – 5-(o-methoxyphenyl)-3-methylpenta-cis-2,trans-4-dienoic acid, mp 165-166°C;
V – 5-(o-methyoxyphenyl)-3-methylpenta-trans-2,trans-4-dienoic acid, mp 191-192°C;
VI – 5-(p-bromophenyl)-3-methylpenta-cis-2,trans-4-dienoic acid, mp 198-199°C;
VII – 5-(p-bromophenyl)-3-methylpenta-trans-2,trans-4-dienoic acid, mp 210-211°C.

SUMMARY

1. A number of aryl analogs of abscissic acid have been obtained by the condensation of substituted benzylideneacetones with ethyl bromoacetate by the Reformatsky reaction. Furyl and other heterocyclic analogs of abscissic acid have been synthesized for the first time by the Wittig reaction of substituted furfurylideneacetones and ketones containing heterocyclic nuclei with ethoxycarbonylmethylenetriphenylphosphorane.

2. It has been found by PMR spectroscopy and also by GLC analysis that the Reformatsky condensation leads predominantly to the formation of the trans,trans isomer in the mixture. The Wittig reaction gives the cis,trans isomer in predominating amount.

3. Biotests have shown that the activities of the analogs synthesized are inferior to the activity of abscissic acid itself.

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