

Synthesis of halo and nitro derivatives of 3-(1-naphthylloxymethylene)phthalide and 3-(2-naphthylloxymethylene)phthalide

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Preparation of halo and nitro derivatives of 3-naphthylloxymethylenephthalides by Gabriel modification of Perkin synthesis from phthalic anhydride and the properly substituted naphthylloxyacetic acid as well as by nitration and halogenation of unsubstituted *E* and *Z* isomers of 3-naphthylloxymethylenephthalides is dealt with. Some of the prepared derivatives have been proved to inhibit plant growth.

Описаны методики получения галоген- и нитропроизводных 3-нафтил-оксиметиленфталидов модификацией синтеза Перкина по Габриелу из фталангидрида и соответствующей замещенной нафтилоксиуксусной кислоты и нитрованием и галогенированием незамещенных *E* и *Z* изомеров 3-нафтилоксиметиленфталидов. Некоторые из полученных производных ингибируют рост растений.

Synthesis of halo and nitro derivatives of 3-naphthylloxymethylenephthalides was carried out in order to examine the optimal conditions and suitability of the method for the preparation of new biologically active compounds. It is known that aryloxymethylenephthalides and their derivatives show significant biological activity, for instance, they inhibit plant growth [1, 2] and stimulate the growth of roots and leaves [3]. These compounds have been reported to possess also insecticidal properties, such as inhibition of juvenile hormones [4, 5].

To prepare the products we used the proved method for the preparation of phthalides, *i.e.* the Gabriel modification of Perkin synthesis. We started from phthalic anhydride and suitably substituted 1- and 2-naphthylloxyacetic acid [6]. This method led, as described in Experimental, to unambiguous results also in the case of preparation of substituted 3-(1-naphthylloxymethylene)phthalides and 3-(2-naphthylloxymethylene)phthalides.

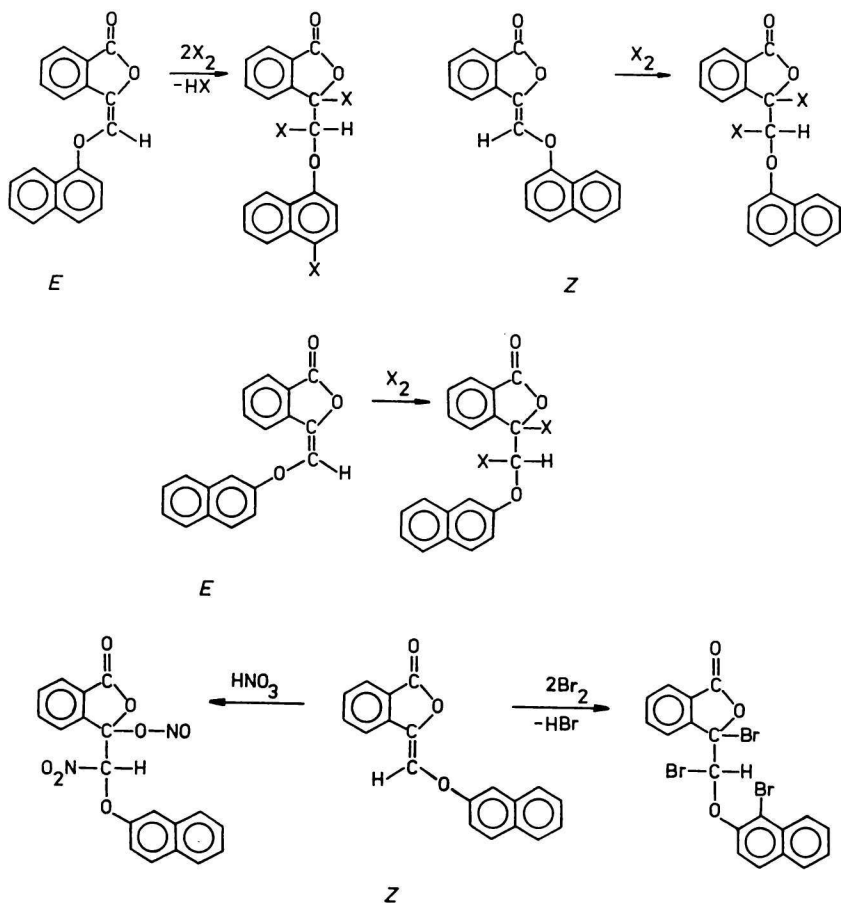
The more stable and less soluble *Z* isomer is present in the product in higher amount. The *E* isomer is present in smaller amount (about 25% of the *Z* isomer) and its isolation is complicated as the reaction is accompanied by formation of

by-products, dark-brown pasty compounds, which are similarly soluble as the *E* isomer. The reactions of naphthylxyacetic acids substituted by halogen or nitro group must be carried out at lower temperatures (by about 20—30°C) than those of the unsubstituted ones.

The second method used for the preparation of new derivatives of phthalides was the halogenation and nitration of 3-(1-naphthylxymethylene)phthalides and 3-(2-naphthylxymethylene)phthalides. We have found that this method did not lead to uniform results. Similar conclusions have been reported in [7—9]. Phthalides, according to the papers mentioned above where nitration and halogenation of benzalphthalide, 3-(1-naphthylmethylene)phthalide, and 3-(2-naphthylmethylene)phthalide have been described, can give substitution and addition products along with products of simultaneous substitution and addition. The authors have found a dependence of the reaction products on the structure of the starting phthalide.

In nitration and halogenation of 3-naphthylxymethylenephthalides we focused our attention on the study of the effect of reaction conditions and structure of the phthalide isomer on the formation of a certain type of the reaction product. In reactions with electrophile agents we used the isolated *E* and *Z* isomers. We have found that, under the conditions described in Experimental, the *E* and *Z* isomers of the phthalides investigated behaved differently. The *Z* isomer of 3-(2-naphthylxymethylene)phthalide by bromination afforded a substitution-addition product while by nitration an addition product only. The *E* isomer of 3-(2-naphthylxymethylene)phthalide reacted with both bromine and nitric acid in addition manner only. Bromination and nitration of the *E* isomer of 3-(1-naphthylxymethylene)phthalide resulted in addition-substitution product and the *Z* isomer gave an addition product only (Scheme 1).

From the obtained experimental data it can be assumed that the investigated phthalides gave by nitration with nitric acid and by bromination with elemental bromine predominantly products of addition to the double bond. We failed to identify the product of substitution on the naphthalene ring only as described by the authors investigating similar reactions with phthalide derivatives based on naphthylacetic acids in [7, 8]. The difference between both types of the starting compounds lies in the oxygen bridge which joins the phthalide cycle with the naphthalene ring. We assume that the difference in the reactivity of both types of compounds is a result of steric release in the region of the double bond by oxygen bridge, which enables a higher addition rate to the double bond and simultaneously also the stability of the isomer. In the reaction with the *E* isomer of 3-(1-naphthylxymethylene)phthalide we supposed the substitution in the position 4 and with the *Z* isomer of 3-(2-naphthylxymethylene)phthalide in the position 1 of the naphthalene ring. We proved this suggestion by comparison of the substitution-addition product with the products of bromination of 3-(4-bromo-1-naphthylxy-



Scheme 1

methylene)phthalide and 3-(1-bromo-2-naphthyloxymethylene)phthalide (Table 1) obtained by direct synthesis. The compounds mentioned above had identical melting points and i.r. spectra.

With some of the prepared compounds inhibition of plant growth has been observed. Herbicidal tests (carried out according to [2] using 2,4-dichlorophenoxyacetic acid as standard) are presented in Table 2. Noticeable activity has been found with the compound V (Table 1).

Table 1

Characteristics of 3-(X-2- and 3-(X-1-naphthylloxymethylene)phthalides

Compound	X	Formula	M	Calculated/found				M.p., °C Solvent	$\nu(\text{C}=\text{O})$ cm^{-1}
				% C	% H	% N	% Halogen		
I	1-Cl	$\text{C}_{19}\text{H}_{11}\text{O}_3\text{Cl}$	322.66	70.72	3.40	—	10.98	184—185	1745
				70.89	3.64		10.73	CH_3COOH	
II	4-Cl	$\text{C}_{19}\text{H}_{11}\text{O}_3\text{Cl}$	322.66	70.72	3.40	—	10.98	186	1720
				70.38	3.24		10.68	CH_3COOH	
III	1-Br	$\text{C}_{19}\text{H}_{11}\text{O}_3\text{Br}$	367.11	62.16	2.99	—	21.76	160—161	1730
				62.32	2.84		21.35	Benzene	
IV	4-Br	$\text{C}_{19}\text{H}_{11}\text{O}_3\text{Br}$	367.11	62.16	2.99	—	21.76	174—175	1755
				62.41	2.48		21.40	Benzene	
V	1-I	$\text{C}_{19}\text{H}_{11}\text{O}_3\text{I}$	414.11	55.10	2.65	—	30.64	153—155	1750
				54.90	2.46		30.60	CCl_4	
VI	4-I	$\text{C}_{19}\text{H}_{11}\text{O}_3\text{I}$	414.11	55.10	2.65	—	30.64	170—171	1726
				54.88	2.41		30.28	CH_3COOH	
VII	4- NO_2	$\text{C}_{19}\text{H}_{11}\text{O}_5\text{N}$	333.21	68.48	3.30	4.20	—	370	1790 NO_2
				68.25	3.11	4.39		$(\text{CH}_3)_2\text{SO}$	$\nu_s(\text{NO}_2)$ 1360 $\nu_{as}(\text{NO}_2)$ 1570

Table 2
Herbicidal activity of 3-naphthyloxymethylenephthalides

Compounds	Test objects											
	<i>Zea mays</i>		<i>Beta vulgaris</i>		<i>Sinapis alba</i>		<i>Fagopyrum vulgare</i>		<i>Triticum aestivum</i>		<i>Pisum sativum</i>	
	A	B	A	B	A	B	A	B	A	B	A	B
I	0	0	0	0	1.5	1	0	0	0	0	1.5	1
II	0	0	2.5	0	2	0	0	0	0	0	1	0
IV	2	1.5	4	1.5	4	1.5	0	0	0	0	2.5	2
V	1.5	1	5	4.5	5	5	4	2	3	2	4.5	4
VI	1.5	1	3.5	3	3	3	0	0	0	0	3.5	3
3-(2-Naphthyloxymethylene)phthalide E isomer [6]	2	1	4.5	4	4.5	4	1.5	0	0	0	3.5	2.5
3-(2-Naphthyloxymethylene)phthalide Z isomer [6]	0	0	3.5	0	4	2	0	0	0	0	2.5	2
Standard	—	2	—	5	—	5	—	2.5	—	2.5	—	5

A — Concentration 10 kg/ha; B — concentration 5 kg/ha, 0—5 degree of inhibition, 5—100% inhibition.

Experimental

Infrared spectra were measured on a UR-20 spectrophotometer (Zeiss, Jena) in the region of 700—2000 cm^{-1} . The apparatus was calibrated by polystyrene foil. The samples were prepared in the form of suspension in paraffin oil (Nujol). The spectrum of Nujol has been compensated.

3-(4-X-1-Naphthyloxymethylene)phthalide (X = Cl, Br, NO_2)

The mixture of remelted phthalic anhydride (15 g; 0.1 mol), 4-X-1-naphthyloxyacetic acid (0.07 mol), and remelted potassium acetate (2.5 g; 0.025 mol) was stirred and heated for 2 h at 185—190°C. The hot reaction mixture was poured into 3% sodium hydrogen carbonate (500 cm^3). After 24 h staying the insoluble precipitate was filtered off and dried. The precipitate was dissolved in cold ethanol (50 cm^3). The insoluble portion was filtered off and crystallized several times from benzene giving the *Z* isomer. The alcoholic solution was evaporated to half volume, diluted with water and the formed precipitate was crystallized from the mixture of ethanol—water (1:1) (*E* isomer). The compounds prepared by this procedure are presented in Table 1.

Nitration of E and Z isomers of 3-(1-naphthyloxymethylene)phthalide

To the nitration mixture, prepared from glacial acetic acid (10 cm^3) and concentrated nitric acid (10 cm^3), the appropriate isomer of phthalide (1 g; 0.004 mol) was added portionwise under stirring at 30°C. After 30 min reaction the yellow precipitate was filtered off, dried, and crystallized from benzene.

The product from *Z* isomer obtained in 94% yield had m.p. 212—216°C (sublimation). For $\text{C}_{19}\text{H}_{12}\text{O}_8\text{N}_2$ (396.3) calculated: 57.59% C, 3.02% H, 7.06% N; found: 57.83% C, 3.29% H, 6.85% N. IR spectrum ($\tilde{\nu}/\text{cm}^{-1}$): $\nu(\text{C}=\text{O})$ 1778, $\nu(\text{C}-\text{O}-\text{C})$ 1270, $\nu_{\text{as}}(\text{NO}_2)$ 1513, $\nu_{\text{s}}(\text{NO}_2)$ 1310.

The product from *E* isomer obtained in 98% yield by crystallization from the mixture of ethanol—water (1:1) were yellow crystals of melting point 81—82°C. For $\text{C}_{19}\text{H}_{11}\text{O}_{10}\text{N}_3$ (441.3) calculated: 51.72% C, 2.49% H, 9.52% N; found: 51.92% C, 2.64% H, 9.37% N. IR spectrum ($\tilde{\nu}/\text{cm}^{-1}$): $\nu(\text{C}=\text{O})$ 1785, $\nu(\text{C}-\text{O}-\text{C})$ 1266, $\nu_{\text{as}}(\text{NO}_2)$ 1513, $\nu_{\text{s}}(\text{NO}_2)$ 1308.

Bromination of E and Z isomers of 3-(1-naphthyloxymethylene)phthalide

Procedure A

To phthalide (1 g) dissolved in chloroform (15 cm^3) bromine (2 g) in chloroform (5 cm^3) was added dropwise under vigorous stirring at 25°C.

Procedure B

The reaction was carried out in chlorobenzene under reflux.

From *Z* isomer (procedure *A*) the precipitate, formed after 1 h, was filtered off and crystallized from benzene. Yield 90%, m.p. 194—195°C.

From *Z* isomer (procedure *B*) the yield of the product was 85%, m. p. 194—195°C. For $C_{19}H_{12}O_3Br_2$ (447.20) calculated: 50.93% C, 2.67% H, 35.63% Br; found: 50.82% C, 2.61% H, 35.30% Br. IR spectrum ($\tilde{\nu}/cm^{-1}$): $\nu(C=O)$ 1740, $\nu(C-O-C)$ 1240.

From *E* isomer (procedure *A*) the product was obtained by evaporation of the reaction mixture to 1/3 volume. After cooling the formed precipitate was crystallized from acetic acid. Yield 86%, m.p. 165—166°C. For $C_{19}H_{11}O_3Br_3$ (527.20) calculated: 43.30% C, 2.08% H, 45.54% Br; found: 43.11% C, 2.29% H, 45.07% Br. IR spectrum ($\tilde{\nu}/cm^{-1}$): $\nu(C=O)$ 1740, $\nu(C-O-C)$ 1240.

Bromination of E and Z isomers of 3-(2-naphthyloxymethylene)phthalide

The precipitate obtained from *Z* isomer by the previous procedure was crystallized from acetic acid. M.p. 194—196°C, yield 82%. For $C_{19}H_{11}O_3Br_3$ (527.2) calculated: 43.30% C, 2.08% H, 45.54% Br; found: 43.02% C, 2.29% H, 45.43% Br. IR spectrum ($\tilde{\nu}/cm^{-1}$): $\nu(C=O)$ 1766, $\nu(C-O-C)$ 1226.

The product obtained from *Z* isomer by the procedure *A* was crystallized from benzene. Yield 70%, m.p. 158°C. For $C_{19}H_{12}O_3Br_2$ (447.2) found: 50.64% C, 3.01% H, 35.94% Br. IR spectrum ($\tilde{\nu}/cm^{-1}$): $\nu(C=O)$ 1743, $\nu(C-O-C)$ 1233.

Nitration of E and Z isomers of 3-(2-naphthyloxymethylene)phthalide

To the nitration mixture, prepared from glacial acetic acid (10 cm³) and nitric acid (10 cm³), phthalide (1 g) was added in small portions under stirring for 15 min at 30°C. After 30 min the yellow precipitate was filtered off, dried, and crystallized from benzene.

The product obtained from *Z* isomer in 84% yield had melting point 224—226°C. For $C_{19}H_{12}O_8N_2$ (396.3) calculated: 57.59% C, 3.02% H, 7.06% N; found: 57.59% C, 3.35% H, 6.72% N. IR spectrum ($\tilde{\nu}/cm^{-1}$): $\nu(C=O)$ 1720, $\nu(C-O-C)$ 1240, $\nu_{as}(NO_2)$ 1513, $\nu_s(NO_2)$ 1360.

The product from *E* isomer was obtained in 80% yield and had melting point 206—208°C (benzene). For $C_{19}H_{12}O_8N_2$ (396.3) calculated: 57.59% C, 3.02% H, 7.06% N; found: 57.52% C, 3.26% H, 6.84% N. IR spectrum ($\tilde{\nu}/cm^{-1}$): $\nu(C=O)$ 1733, $\nu(C-O-C)$ 1240, $\nu_{as}(NO_2)$ 1513, $\nu_s(NO_2)$ 1350.

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