On Phthalides and 1,3-Indandiones. XLIII.* Preparation of 2-(1-Naphthyl)-1,3-indandiones and 2-(2-Naphthyl)-1,3-indandiones Substituted in Position 5 of the Indandione Ring and in Position 4(1) of the Naphthalene Ring

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Dedicated to Professor Dr. Ján Kubis on the occasion of his 60th birthday

The preparation of 5-X-2-(4-Y-1-naphthyl)-1,3-indandiones and 5-X-2-(1-Y-2-naphthyl)-1,3-indandiones from the corresponding phthalides by rearrangement with sodium methoxide in methanol as well as by condensation of 4-X-phthalic anhydrides with 1-naphthylacetic acid and 2-naphthylacetic acid, respectively, in the presence of triethylamine is described. The starting 5(6)-X-3-(1-Y-2-naphthal)phthalides were obtained by chlorination, bromination, and nitration of 5(6)-X-3-(2-naphthal)phthalides.

The present work is connected with our previous papers concerned with the study of relationship between the structures of 1,3-indandione derivatives and their anticoagulating activity [1—3]. We found earlier [3] that the introduction of a substituent into the indandione skeleton of 2-(Y-phenyl)-1,3-indandiones induces a decrease or a complete disappearance of their anticoagulating activity in comparison with the activity of the starting substances. We also wanted to find out whether similar relationship was valid for 5-X-2-(4-Y-1-naphthyl)-1,3-indandiones as (4-Y-1-naphthyl)-1,3-indandiones had significant anticoagulating properties. Besides, we prepared 5-X-2-(1-Y-2-naphthyl)-1,3-indandiones to see whether the introduction of substituents would induce anticoagulating properties of the 2-(2-naphthyl)-1,3-indandione which itself had no such properties [4].

We have prepared 5-X-2-(1-naphthyl)-1,3-indandiones (X = Cl, Br, NO_2; substances *I*, *IV*, *VIII*) and 5-X-2-(2-naphthyl)-1,3-indandiones (X = Cl, Br; substances *XVIII* and *XXII*) by condensation of 4-X-phthalic anhydride with 1-naphthylacetic acid and 2-naphthylacetic acid, respectively, in acetic anhydride and triethylamine (Chart 1) and by rearrangement of 5(6)-X-3-(1-naphthal)phthalides and 5(6)-X-3-(2-naphthal)phthalides, respectively. Only in case 0.01 mole of 4-X-phthalic anhydride and 0.01 mole of naphthylacetic acid were treated with 0.03 mole of triethylamine in acetic anhydride, the main reaction product was the ap-

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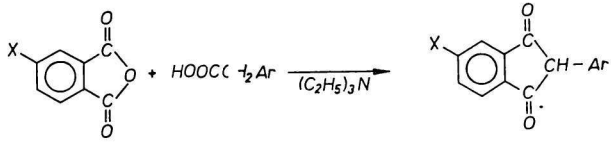
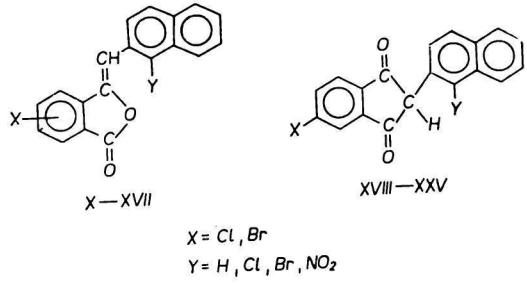
propriate derivative of 2-aryl-1,3-indandiones. By decreasing the temperature and quantity of triethylamine, greater quantity of phthalide was obtained. 5-X-2-(4-Y--1-Naphthyl)-1,3-indandiones (X = Cl, Br, Y = Cl, Br, NO_2; substances *II*, *III*, *V*, *VI*, *VII*) were prepared from 5(6)-X-3-(4-Y-1-naphthal)phthalides by rearrangement with sodium methoxide in methanol [5]. 5-Amino-2-(1-naphthyl)-1,3--indandiones (*IX*) were prepared by reduction of *VIII*.



We are presenting the preparation of 5(6)-X-3-(1-Y-2-naphthal)phthalides used as starting substances for the preparation of indandiones as it has not been described till now. The mentioned phthalides were obtained by condensation of 4-X-phthalic anhydride (X = Cl, Br) with 2-naphthylacetic acid similarly as at the preparation of 5(6)-X-3-benzalphthalides [6]. Also in this case, both positional isomers possible, 5-X-3-(2-naphthal)phthalide (substance *a*) and 6-X-3-(2-naphthal)phthalide (substance *b*), were formed (Chart 2).



The isomer of a higher m.p. was obtained in more than 75—80% of the total yield and we assumed that it was the isomer 5 (formed by reaction on the carbonyl carbon in *m*-position with regard to the halogen). This assumption was in agreement with the results of [5, 6] where condensation of the mentioned anhydrides with 1-naphthylacetic acid and phenylacetic acid, respectively, gave larger quantities of the isomer 5 than those of isomer 6. The presented assumption about the structure of these isomers was supported by infrared spectroscopy. The absorption band belonging to the stretching vibration of carbonyl group of the isomers of higher m.p. was shifted 6 or 7 cm^{-1} to the lower wave numbers with regard to the wave numbers of carbonyl group of the isomers of lower m.p. (see Table 2). This is in agreement with the effect of the halogen in the *p*-position (isomer 5) and in the *m*-position (isomer 6) on the position of the absorption band of carbonyl group. It is also in agreement with the values found for 5-bromo-3-benzalphthalide and 6-bromo--3-benzalphthalide [7].

The positional isomers were separated chromatographically on silica gel. Benzene or the mixture of chloroform—ethanol (3 : 1) were used as eluents. The isomers could be separated by fractional crystallization from the mixture chloroform—ethanol as well. The isomer 5 was less soluble.

Halogenation and nitration of 5(6)-X-3-(2-naphthal)phthalide were carried out by methods which were used for the preparation of analogous unsubstituted (2--naphthal)phthalide [8]. Chlorination with sulfurylchloride in chloroform proceeded without difficulties similarly as in the case of (2-naphthal)phthalide. Bromination of 5(6)-X-3-(2-naphthal)phthalide was different from that of (2-naphthal)phthalide. Whereas an addition bromination was the result of the treatment of (2-naphthal)-phthalide with one molequivalent of bromine in chloroform at room temperature, a substitution bromination proceeded on the naphthalene ring at substances *X* and

Table 1

Analytical data of the prepared 5-X-2-(4-Y-1-naphthyl)-1,3-indandiones

Compound	X	Y	Formula	*M*	Calculated/found				M.p. [°C]	ν(CO) [cm^{-1}]
					% C	% H	% X	% Y		
I	Cl	H	$C_9H_{11}O_2Cl$	306.7	74.53	3.26	11.56		178—179	1740
					74.82	3.25	11.32			1699
II	Cl	Cl	$C_9H_{10}O_2Cl_2$	341.2	66.91	2.93	10.39	10.39	165—167	1744
					66.58	3.21	10.25	10.25		1712
III	Cl	Br	$C_9H_{10}O_2ClBr$	385.6	59.15	2.65	9.19	20.72	169—171	1745
					59.32	2.68	9.32	20.95		1713
IV	Br	H	$C_9H_{11}O_2Br$	351.2	64.68	2.84	22.75		183—185	1742
					64.31	3.05	22.31			1698
V	Br	Cl	$C_9H_{10}O_2BrCl$	385.6	59.15	2.65	20.72	9.19	141—143	1746
					58.91	2.38	20.65	9.05		1708
VI	Br	Br	$C_9H_{10}O_2Br_2$	430.1	53.07	2.32	18.58	18.58	182—184	1745
					52.73	2.75	18.72	18.72		1706
VII	Br	NO_2	$C_9H_{10}O_4BrN$	396.2	57.62	2.52	20.31	3.75 (N)	128—129	1745
					57.35	2.68	20.25	3.68 (N)		1712
VIII	NO_2	H	$C_9H_{11}O_4N$	317.34	71.98	3.15	4.42 (N)		201—202	1709
					72.25	3.25	4.31 (N)			1667
IX	NH_2	H	$C_9H_{13}O_2N$	287.3	79.47	3.48	4.54 (N)		235—236	1739
					79.81	3.25	4.68 (N)			1695

XI under the same conditions. Nitration was carried out with fuming nitric acid in chloroform. Evidence for the position of the halogen and nitro group on the naphthalene skeleton was obtained in a similar manner as at the analogous (2-naph-thal)phthalide derivatives [8], *i.e.* by oxidation with potassium dichromate and sulfuric acid in glacial acetic acid to the corresponding naphthoic acids. In all cases we found that the reaction proceeded in the position 1, *i.e.* we obtained 5(6)-X-3--(1-Y-2-naphthal)phthalides (X = Cl, Br, Y = Cl, Br, NO_2; *XII—XVII*). Rearrangement of the substances *X—XVII* by sodium methoxide in methanol gave the corresponding 5-X-2-(1-Y-2-naphthyl)-1,3-indandiones.

Hypoprothrombinaemic effect of the prepared indandiones was investigated on the rats by Quick's monophasic method in the periods of 24 hours. Comparison of 5-X-2-(4-Y-1-naphthyl)-1,3-indandiones with 2-(4-Y-1-naphthyl)-1,3-indandiones

Table 2

Analytical data of the 5(6)-X-3-(1-Y-2-naphthal)phthalides

Compound	X	Y	Formula	*M*	Calculated/found % C	% H	% X	% Y	M.p. [°C]	ν(C=C) [cm^{-1}]	ν(CO) [cm^{-1}]
Xa	5-Cl	H	$C_9H_{11}O_2Cl$	306.7	74.53	3.26	11.56		201–203	1669	1478
					74.68	3.43	11.83				
Xb	6-Cl	H	$C_9H_{11}O_2Cl$	306.7	74.53	3.26	11.56		172–174	1668	1772
					74.25	3.18	11.42				
XIa	5-Br	H	$C_9H_{11}O_2Br$	351.2	64.68	2.84	22.75		231–232	1668	1781
					64.36	2.91	22.36				
XIb	6-Br	H	$C_9H_{11}O_2Br$	351.2	64.68	2.84	22.75		194–195	1667	1776
					64.72	3.12	22.83				
XIIa	5-Cl	Cl	$C_9H_{10}O_2Cl_2$	341.2	66.91	2.93	19.39	10.39	248–250	1658	1792
					67.13	2.68	10.81	10.81			
XIIIa	5-Cl	Br	$C_9H_{10}O_2ClBr$	385.6	59.15	2.65	9.19	20.72	270–271	1659	1791
					59.38	2.83	9.36	21.20			
XIIIb	5-Cl	Br	$C_9H_{10}O_2ClBr$	385.6	59.15	2.65	9.19	20.72	228–229	1658	1787
					58.96	2.83	9.25	20.93			
XIVa	5-Cl	NO_2	$C_9H_{10}O_4ClN$	351.7	64.68	2.84	10.8	3.97 (N)	258–260	1677	1798
					64.75	2.95	10.98	4.25 (N)			
XVa	5-Br	Cl	$C_9H_{10}O_2ClBr$	341.2	59.15	2.65	20.77	9.19	269–271	1662	1793
					59.48	2.89	20.95	9.26			
XVIa	5-Br	Br	$C_9H_{10}O_2Br_2$	430.1	53.07	2.32	18.58	18.58	297–298	1659	1791
					53.43	2.68	18.74	18.74			
XVIb	6-Br	Br	$C_9H_{10}O_2Br_2$	430.1	53.07	2.32	18.58	18.58	249–251	1658	1787
					53.23	2.48	18.65	18.65			
XVIIa	5-Br	NO_2	$C_9H_{10}O_4BrN$	396.2	57.62	2.52	20.31	3.75 (N)	278–280	1661	1798
					57.81	2.84	20.17	3.84 (N)			

Table 3

Analytical data of the 5-X-2-(1-Y-2-naphthyl)-1,3-indandiones

Compound	X	Y	Formula	*M*	Calculated/found % C	% H	% X	% Y	M.p. [°C]	ν(CO) [cm^{-1}]
XVIII	Cl	H	$C_9H_{11}O_2Cl$	306.7	74.53	3.26	11.56		135–137	1710
					74.63	3.18				1642
XIX	Cl	Cl	$C_9H_{10}O_2Cl_2$	341.2	66.91	2.93	10.39	10.39	127–129	1740
					66.51	2.71	10.15	10.15		1712
XX	Cl	Br	$C_9H_{10}O_2BrCl$	385.6	59.15	2.65	9.19	20.72	125–127	1743
					58.93	2.87	9.38	21.05		1718
XXI	Cl	NO_2	$C_9H_{10}O_4ClN$	351.7	64.68	2.68	10.8	3.97 (N)	97–99	1728
					64.32	2.35	10.75	3.64 (N)		1688
XXII	Br	H	$C_9H_{11}O_2Br$	351.2	64.68	2.68	22.75		148–151	1702
					64.45	2.94	22.38			1643
XXIII	Br	Cl	$C_9H_{10}O_2BrCl$	385.6	59.15	2.65	20.72	9.19	131–133	1741
					59.43	2.78	20.51	9.03		1708
XXIV	Br	Br	$C_9H_{10}O_2Br_2$	439.1	53.07	2.32	18.58	18.58	129–131	1748
					53.24	2.45	18.31	18.31		1710
XXV	Br	NO_2	$C_9H_{10}O_4BrN$	396.2	57.62	2.52	20.31	3.75 (N)	106–108	1720
					57.35	2.74	20.48	4.01 (N)		1683

showed that the anticoagulating activity of the derivatives substituted on the indandione skeleton decreased (in the case of the substance *IX* totally disappeared). These findings are in agreement with our previous work [3]. 5-X-2-(1-Y-2-Naphthyl)--1,3-indandiones showed no anticoagulating properties. Pharmacological part will be published elsewhere in detail.

Experimental

Melting points (Kofler) and analytical data of the prepared compounds are presented in Tables 1, 2, and 3.

The infrared spectra were recorded on a double-beam spectrophotometer model UR-20. Samples were measured as Nujol mulls (4 mg substance: 15 mg Nujol). The calibration was checked against the spectrum of polystyrene foil.

5-X-2-(4-Y-1-Naphthyl)-1,3-indandione

Method *A* — for X = Cl, Br, NO_2; Y = H (*I*, *IV*, *VIII*)

0.05 mole of 4-X-phthalic anhydride, 0.05 mole of 1-naphthylacetic acid, 0.2 mole of acetic anhydride, and 0.15 mole of dry triethylamine were placed into a 250-ml flask provided with a reflux condenser. The reaction mixture was heated at 125—130°C for 45 minutes and then the volatile compounds were distilled off under the reduced pressure. To the distillation residue 50 ml of 96% ethanol was added, the solution was boiled and poured into 1000 ml of 2% sodium hydroxide. The reaction mixture was then stirred for 6—8 hours at 30°C and filtered. The filtrate was acidified with 20% hydrochloric acid to pH 2—3. The crude product was crystallized from ethanol. (Yield 45—50%.)

Method *B* — for X = Cl, Br, NO_2; Y = H, Cl, Br (*I*—*VIII*)

In a 250-ml flask containing 120 ml of 10% methanolic solution of sodium methoxide, the proper 5(6)-X-3-(4-Y-1-naphthal)phthalide [5] was placed. The reaction mixture was heated under reflux for 3 hours. The solution was then cooled, filtered and acidified with 20% hydrochloric acid. The crude product was crystallized from ethanol in 80—93% yield.

5-Amino-2-(1-naphthyl)-1,3-indandione (IX)

In a 250-ml three-necked flask provided with a mechanical stirrer, a reflux condenser, and a gas inlet tube, 10 g of stannous dichloride ($SnCl_2 \cdot 2H_2O$), 100 ml of acetic acid, 3.2 g (0.01 mole) of 5-nitro-2-(1-naphthyl)-1,3-indandione (*VIII*) were placed and hydrogen chloride was introduced into the reaction mixture for two and a half hours at 60°C. The reaction mixture was then cooled and poured into 150 ml of water. A salt was formed out of which the free amine was recovered by washing with ammonia. (Yield 2.25 g, 75%.)

5(6)-X-3-(2-Naphthal)phthalide

X = Cl (*X*); X = Br (*XI*)

In a 100-ml round-bottomed flask provided with water outlet tube, 0.05 mole of 4-X-phthalic acid (X = Cl, Br) was placed and heated to 230°C for 25 minutes. After cooling to 160—180°C, 0.05 mole of 2-naphthylacetic acid and 0.5 g of freshly fused

potassium acetate were added and heated to 220°C for 2 hours. The reaction mixture was then poured into 50—70 ml of ethanol. The positional isomers were separated either chromatographically on silica gel (Siloxid, particle size 5—30 nm, Association of the Chemical and Metallurgical Production, Ústí nad Labem) without activation when the eluents used were benzene or chloroform—ethanol (3 : 1) or by fractional crystallization from the mixture of chloroform—ethanol (derivatives substituted in the position 5 were less soluble). The total yield of *X* was 9 g (60%), from that *Xa* 78%, and that of *XI* was 9.7 g (55%), from that *XIa* 75%.

5-X-3-(1-Chloro-2-naphthal)phthalide

X = Cl (*XIIa*); X = Br (*XVa*)

To 0.03 mole of 5-X-3-(2-naphthal)phthalide (X = Cl, Br; *Xa*, *XIa*) dissolved in 100 ml of chloroform, 5 g of freshly distilled sulfurylchloride was added. The reaction mixture was boiled and allowed to react for 30 minutes. Then 100 ml of ethanol was added and the crystals formed were recrystallized from the chloroform—ethanol mixture. (Yield 62%.)

5(6)-X-3-(1-Bromo-2-naphthal)phthalide

X = Cl (*XIIIa*, *XIIIb*); X = Br (*XVIa*, *XVIb*)

0.02 mole of 5(6)-X-3-(2-naphthal)phthalide (*Xa*, *XIa*, *Xb*, *XIb*) was dissolved in 60 ml of chloroform and molequivalent of bromine in 20 ml of chloroform was added at room temperature. Then 200 ml of ethanol was added over a period of 20 minutes and the crystals formed were recrystallized from the ethanol—chloroform mixture. (Yield 75—79%.)

5-X-3-(1-Nitro-2-naphthal)phthalide

X = Cl (*XIVa*); X = Br (*XVIIa*)

0.01 mole of 5-X-3-(2-naphthal)phthalide was dissolved in 50 ml of chloroform, heated to boiling point and 6 ml of nitric acid (specific gravity 1.5) was added within 45 minutes. A yellow precipitate was washed with ethanol and recrystallized from chloroform. (Yield 76%.)

5-X-2-(1-Y-2-Naphthyl)-1,3-indandione

X = Cl, Br; Y = H, Cl, Br, NO_2 (*XVIII—XXV*)

The process of preparation is analogous to that given for substances *I—VIII*. (Yield 85—91%.)

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