On Phthalides and 1,3-Indandiones. XXXII.* Preparation and Reactions of 5(6)-Chloro-3-(naphthal-1′)-phthalide and 5(6)-Bromo-3-(naphthal-1′)phthalide

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The preparation of 5-X-3-(naphthal-1′)phthalide and 6-X-3-(naphthal-1′)phthalide (X = Cl, Br) is described either by the condensation of 4-X-phthalic anhydride with 1-naphthylacetic acid, or *via* 5-nitro-3-(naphthal-1′)phthalide and 6-nitro-3-(naphthal-1′)phthalide. The phthalides thus prepared were subjected to the electrophilic substitution reactions on the naphthalene ring; the substitution was found to occur at position 4′.

As known, groups of X—CH=CH— type attached to the benzene ring orientate a new substituent in electrophilic substitution reactions preponderantly to *p*-position. The reaction rate in substitution reactions is lower in most cases when compared with this of unsubstituted benzene [1]. It is not known how this type of bonded groups influences electrophilic substitution reactions on naphthalene nucleus. For this reason, we attempted electrophilic substitution reactions on naphthalene nucleus to which various substituted phthalidylene groups were attached. This project extends our papers [2, 3] referring to electrophilic substitution reactions of α-naphthalphthalide and β-naphthalphthalide; it has been found that the substitution take place in 4′ and 1′ position, respectively.

In connection with this problem, we have prepared 5-chloro-3-(naphthal-1′)-phthalide (*Ia*), 6-chloro-3-(naphthal-1′)phthalide (*Ib*), 5-bromo-3-(naphthal-1′)-phthalide (*IIa*) and 6-bromo-3-(naphthal-1′)phthalide (*IIb*) as starting material by Gabriel modification of Perkin synthesis, *i.e.* by the condensation of 4-chlorophthalic anhydride, or 4-bromophthalic anhydride with 1-naphthylacetic acid in the presence of potassium acetate as catalyst. Even in this case, similarly as in the condensation of these anhydrides with phenylacetic acid [4—6], both position isomers were obtained with halogen in the position 5 (denominated by the letter *a*) and 6 (denominated by the letter *b*).

Separation of position isomers formed in this reaction was carried out in toluene, benzene, in the mixture chloroform—ethanol, the different solubility of those solvents being exploited. 5-Halonaphthalphthalides are formed in higher percentage in this reaction (Table 1). The structure of substances *Ia*, *Ib*, *IIa*, *IIb* was derived from the known structure of 6-nitro-3-(naphthal-1′)phthalide, prepared by condensation [7] of 6-nitrophthalide with 1-naphthalenecarbaldehyde in 1,2,4-trichlorobenzene in the presence of piperidine as catalyst. Because of the very poor yield (2%) of this reaction, 6-nitro-3-(naphthal-1′)phthalide was prepared by Oglialoro method modified for this purpose. It is worth noting that even using the Gabriel modification of Perkin synthesis, the condensation of 4-nitrophthalic anhydride with

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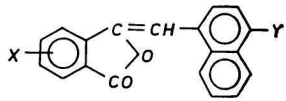
Table 1



Compound	X	Y	Yield %	*M*	M.p. (Kofler)	Calculated/found % C	% H	% X	% Y	ν(C=C) cm^{-1}	ν(C=O) cm^{-1}
Ia	5—Cl	H	23.1	306.7	224—226	74.53	3.26	11.56		1660	1771
						74.60	3.18	11.83			
Ib	6—Cl	H	6.5	306.7	246—248	74.53	3.26	11.56		1666	1776
						74.05	3.32	11.76			
IIa	5—Br	H	24.5	351.2	195—197	64.68	2.84	22.75		1658	1764
						64.45	2.96	22.53			
IIb	6—Br	H	10.1	351.2	238—240	64.68	2.84	22.75		1656	1770
						64.53	3.11	22.50			
IIIa	5—NO_2	H	13.2	317.3	269—271	71.98	3.15	4.42(N)		1647	1774
						72.18	3.18	4.31(N)			
IIIb	6—NO_2	H	23.1	317.3	293—295	71.98	3.15	4.42(N)		1644	1787
						71.85	3.26	4.54(N)			
IVa	5—NH_2	H	85.4	287.3	220—221	79.47	3.48	4.93(N)		1668	1785
						79.63	3.66	5.20(N)			
IVb	6—NH_2	H	81.3	287.3	250—252	79.48	3.48	4.93(N)		1672	1761
						79.42	3.54	5.19(N)			
Va	5—Cl	Cl	60.4	341.2	254—256	66.91	2.93	10.39	10.39	1666	1775
						67.08	3.16	10.42	10.42		
VIa	5—Cl	Br	76.4	385.6	274—276	59.15	2.65	9.19	8.50	1658	1778
						58.96	2.68	9.31	8.68		
VIIa	5—Cl	NO_2	64.0	351.7	281—282	64.68	2.84	10.8	3.97(N)	1657	1789
						64.51	2.93	10.25	4.13(N)		
VIIIa	5—Br	Cl	68.5	385.6	290—292	59.15	2.65	20.72	9.19	1664	1773
						60.11	2.73	20.74	9.20		
VIIIb	6—Br	Cl	61.1	385.6	271—272	59.15	2.65	20.72	9.19	1658	1758
						60.15	2.58	20.48	9.15		
IXa	5—Br	Br	71.8	430.1	284—286	53.07	2.32	18.58	18.58	1654	1770
						53.24	2.41	18.41	18.41		
IXb	6—Br	Br	69.3	430.1	266—268	53.07	2.32	18.58	18.58	1660	1759
						52.91	2.58	18.45	18.45		
Xa	5—Br	NO_2	81.0	396.2	309—310	57.62	2.52	20.17	3.75(N)	1657	1775
						57.58	2.68	20.31	3.99(N)		
Xb	6—Br	NO_2	61.0	396.2	289—290	57.62	2.52	20.17	3.75(N)	1651	1774
						57.84	2.43	20.15	3.80(N)		

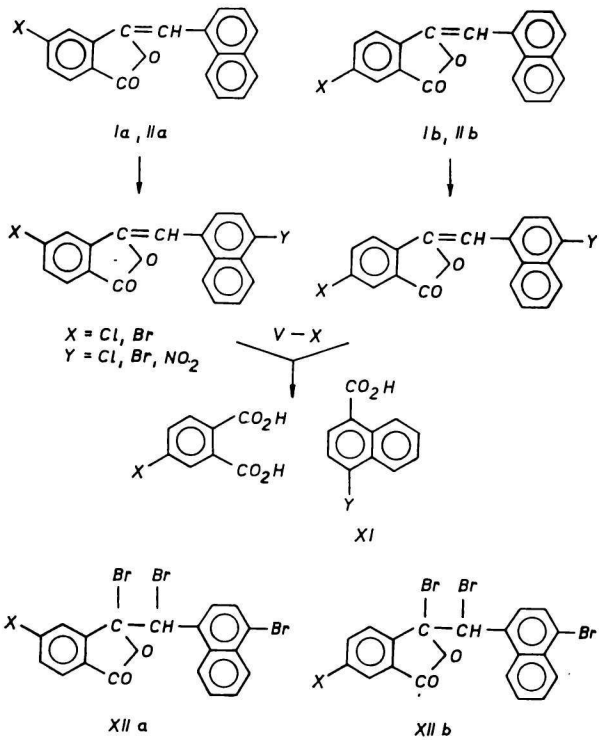
1-naphthylacetic acid afforded the proper naphthalnitrophthalides in a very poor yield (3—4%) only. The yield of reactions carried out by Oglialoro method which is described in the experimental part in detail was disproportionately higher (36.5%). However, both position isomers are formed in this case, both being well separated by fractionated crystallization from dioxan. The less soluble isomer has its melting point (293—295°C) identical with this one prepared according to [7], thereby being 6-nitro-3-(naphthal-1′)phthalide (*IIIb*). The mixed m.p. of this isomer with phthalide prepared according to [7] does not reveal depression. The second isomer should be 5-nitro-3-(naphthal-1′)phthalide (*IIIa*).

The structure of *Ia*, *Ib*, *IIa*, *IIb* was elucidated as follows: Upon reduction with stannous chloride in acetic acid, *IIIa* afforded 5-amino-3-(naphthal-1′)phthalide (*IVa*), whereas *IIIb* afforded 6-amino-3-(naphthal-1′)phthalide (*IVb*). Sandmeyer reaction of diazonium salt of 5-amino-3-(naphthal-1′)phthalide led to 5-chloro--3-(naphthal-1′)phthalide (*Ia*) and 5-bromo-3-(naphthal-1′)phthalide (*IIa*) the melting points of which corresponded to the isomers of lower melting point prepared by condensation. 6-Chloro-3-(naphthal-1′)phthalide (*Ib*) and 6-bromo-3-(naphthal-1′)-phthalide (*IIb*) were prepared from 6-amino-3-(naphthal-1′)phthalide, in analogical way; they corresponded to isomers with higher m.p. The mixed m.p. of compounds prepared in such a way did not exhibit depression with those prepared by Gabriel modification of Perkin synthesis.

Of electrophilic substitution reactions chlorination, bromination and nitration was carried out with substances *Ia*, *IIa*, *IIb*.

Likewise to our preceding papers [2, 3], the chlorination was carried out with sulfurylchloride which was first suggested by us to be of use in electrophilic chlorinations of naphthalene ring. Sulfurylchloride is nowadays reported to be a chlorination reagent for benzene derivatives [8]. Chlorination of substances *Ia*, *IIa* and *IIb* led to 5-chloro-3-(4′-chloronaphthal-1′)phthalide (*Va*), 5-bromo-3-(4′-chloronaphthal--1′)phthalide (*VIIIa*) and 6-bromo-3-(4′-chloronaphthal-1′)phthalide (*VIIIb*), respectively.

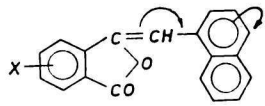
The bromination was carried out with elemental bromine. If the mentioned naphthalphthalides are treated with one molequivalent of bromine, the substitution



on the naphthalene ring takes place preferentially in the 4′ position and substances *Ia*, *IIa*, *IIb* afford 5-chloro-3-(4′-bromonaphthal-1′)phthalide (*VIa*), 5-bromo-3-(4′-bromonaphthal-1′)phthalide (*IXa*) and 6-bromo-3-(4′-bromonaphthal-1′)-phthalide (*IXb*). When treated with one more molequivalent bromine an addition to the double bond occurs and 5-chloro-3-(4′-bromonaphthal-1′)phthalide dibromide (*XIa*), 5-bromo-3-(4′-bromonaphthal-1′)phthalide dibromide (*XIIa*) and 6-bromo-3-(4′-bromonaphthal-1′)phthalide dibromide (*XIIb*) are formed.

Nitration of substances *Ia*, *IIa*, *IIb* in chloroform proceeds with higher yields than that in acetic acid. We are feeling the need to point out that the use of a larger amount of nitric acid lowers the yield.

The position of the substituent attached to the naphthalene ring was determined by oxidation by potassium bichromate to the proper naphthoic acids. Derivatives substituted in position 4 were obtained in all cases. Keeping the course of the substitution reactions in mind it can be assumed that the determinig factor influencing and orientating the substituent entering the naphthalene skeleton of naphthalides substituted on the naphthalene skeleton by halogene, is the interaction of the π-electron cloud of the double bond with that of the naphthalene ring.



X = Cl, Br

This is the only way how to explain the electrophilic substitution reaction of possible α-positions of the naphthalene ring exactly in position 4.

To prove the structure of the prepared phthalides, infra-red spectra were measured. Our attention was paid to frequencies of the C=O and C=C bond which are influenced by the character and position of the substituents.

Experimental

5-X-3-(Naphthal-1′)phthalide and 6-X-3-(naphthal-1′)phthalide X = Cl (*Ia*, *Ib*); Br (*IIa*, *IIb*)

0.1 mole of 4-X-phthalic acid was placed into a 100 ml round bottomed flask provided with a water outlet tube and heated at 230°C for 25 minutes. After cooling to 160—180°C, 1-naphthylacetic acid (18.6 g, 0.1 mole) and freshly fused potassium acetate (1 g) was added and heated at 220—230°C for additional two hours. The reaction mixture was then poured into 100 ml ethanol. Position isomers were separated by fraction crystallization from chloroform, benzene and toluene. 5-Isomers are more soluble.

5-Nitro-3-(naphthal-1′)phthalide (IIIa) and 6-nitro-3-(naphthal-1′)phthalide (IIIb)

4-Nitrophthalic acid (21.1 g, 0.1 mole) was heated in acetic anhydride (200 ml) for 45 minutes. To this solution first anhydrous potassium carbonate (6.9 g) and then 1-naphthylacetic acid (18.6 g, 0.1 mole) were added. The reaction mixture was heated

at 125—135°C for 8 hours. At the end of this reaction the proper nitrophthalides separate, the reaction mixture was cooled, then poured into cold water (1 l) and allowed to stand for 5 hours. The raw product was purified by fraction crystallization from dioxan. 6-Nitro-3-naphthalphthalide is less soluble.

5-Amino-3-(naphthal-1')phthalide (IVa)

Stannous chloride (22.5 g, 0.1 mole), acetic acid (150 ml) and 5-nitro-3-(naphthal-1')-phthalide was placed to a 250 ml three-necked flask provided with a reflux condenser and mechanical stirrer. The reaction was carried out at 80°C for three hours, hydrogen chloride being introduced. A salt is formed out of which amine was recovered by washing with ammonia. The raw amine was crystallized from acetic acid.

6-Amino-3-(naphthal-1')phthalide (IVb)

Substance *IVb* could be obtained in analogous way as the substance *IVa* starting from 6-nitro-3-(naphthal-1')phthalide.

5-Chloro-3-(naphthal-1')phthalide

5-Amino-3-(naphthal-1')phthalide (0.01 mole) in a 200 ml flask was suspended in concentrated hydrochloric acid (50 ml), cooled to 5°C and $NaNO_2$ (0.75 g) was added while stirring. The suspension was allowed to stand for one hour, then cuprous chloride (prepared from $CuSO_4 \cdot 5H_2O$ (5.2 g), NaCl (135 g), $Na_2S_2O_3 \cdot 5H_2O$ (1.1 g) and NaOH (0.75 g)) was added and heated on a steam bath for 30 minutes. The reaction mixture was diluted with 150 ml water. 5-Chloro-3-(naphthal-1')phthalide was obtained from the raw product by crystallization from chloroform in 38.2% yield.

6-Chloro-3-(naphthal-1')phthalide

The procedure is the same as described for 5-chloro-3-(naphthal-1')phthalide. Yield 31.2%.

5-Bromo-3-(naphthal-1')phthalide

5-Amino-3-(naphthal-1')phthalide (0.01 mole) was suspended in 47% hydrobromic acid (70 ml) and cooled to 5°C. $NaNO_2$ (0.75 g) was added while stirring. After one-hour standing at 10—15°C, cuprous bromide (freshly prepared from $CuSO_4 \cdot 5H_2O$ (5.2 g), NaBr (2.2 g), $Na_2S_2O_3 \cdot 5H_2O$ (1.1 g) and NaOH (0.75 g)) was added to the suspension. Proceeded further as described for 5-chloro-3-(naphthal-1')phthalide. Yield 33.2%.

6-Bromo-3-(naphthal-1')phthalide

The procedure is analogous to that given for 5-bromo-3-(naphthal-1')phthalide. Yield 31.8%.

5-X-3-(4'-Chloronaphthal-1')phthalide
X = Cl (*Va*); Br (*VIIIa*)

To 5-X-3-(naphthal-1')phthalide (0.028 mole) dissolved in chloroform (150 ml), sulfurylchloride (5.5 g, 0.041 mole) in chloroform (30 ml) was added stepwise. The reaction

mixture was heated under reflux condenser for 1/2 hour and then one half of chloroform was distilled off. The most part of 5-X-3-(4′-chloronaphthal-1′)phthalide was being separated while the remaining part was obtained by adding 50 ml ethanol. The raw product was crystallized from chloroform.

6-Bromo-3-(4′-chloronaphthal-1′)phthalide (VIIIb)

The procedure is analogous to that given for preparation of substances *IVa* and *Va*.

5-X-3-(4′-Bromonaphthal-1′)phthalide
X = Cl (*VIa*); Br (*IXa*)

To 5-X-3-(naphthal-1′)phthalide (0.028 mole) dissolved in chloroform (200 ml), molequivalent of bromine in chloroform (50 ml) was added at room temperature. The reaction mixture was allowed to stand for 1/2 hour. The yellow 5-X-3-(4′-bromonaphthal-1′)-phthalide which separates was filtered off by suction, washed with ethanol and crystallized from chloroform.

6-Bromo-3-(4′-bromonaphthal-1′)phthalide (IXb)

This product was prepared analogously as given for 5-X-3-(4′-bromonaphthal-1′)-phthalide.

5-X-3-(4′-Bromonaphthal-1′)phthalide dibromide
X = Cl (*XIa*); Br (*XIIa*)

To 5-X-3-(naphthal-1′)phthalide (0.028 mole) in chloroform (150 ml) two molequivalents (9.38 g) of bromine in chloroform (50 ml) were added while stirring during 10 minutes at room temperature. 5-X-3-(4′-Bromonaphthal-1′)phthalide dibromide which separates within 30 minutes was crystallized from chloroform.

5-Chloro-3-(4′-bromonaphthal-1′)phthalide dibromide forms white crystals, m.p. 216—218°C (Kofler). Yield 72.4%.

For $C_{19}H_{10}O_2ClBr_3$ (545.25) calculated: 42.13% Br, 6.5% Cl; found: 41.86% Br, 6.91% Cl; ν(CO) 1786 cm^1.

5-Bromo-3-(4′-bromonaphthal-1′)phthalide dibromide forms white crystals, m.p. 223—225°C (Kofler). Yield 69.9%.

For $C_{19}H_{10}O_2Br_4$ (590.03) calculated: 53.9% Br, found: 53.85% Br; ν(CO) 1785 cm^{-1}.

6-Bromo-3-(4′-bromonaphthal-1′)phthalide dibromide (XIIb)

The product was prepared in a similar way as given for *XIIa*. Yield 71.2 %.

For $C_{19}H_{10}O_2Br_4$ (590.03) calculated: 53.9% Br, found: 53.6% Br; ν(CO) 1783 cm^{-1}.

5-X-3-(4-Nitronaphthal-1′)phthalide
X = Cl (*VIIa*); Br (*Xa*)

5-X-3-(Naphthal-1′)phthalide (X = Cl, Br; 0.028 mole) was dissolved in chloroform (400 ml) in a 750 ml flask provided with a reflux condenser, heated to boiling point and nitric acid (10 ml, specific gravity 1.5) was added within 20 minutes. During the reaction a yellow substance precipitates of the solution. The reaction product was crystallized from chloroform.

6-Bromo-3-(4'-nitronaphthal-1')phthalide (Xb)

The process of preparation is similar to that of 5-X-3-(4'-nitronaphthal-1')phthalide.

4-Y-Naphthoic acids (XIII)
Y = Cl, Br, NO_2

5-X-3-(4'-Y-Naphthal-1')phthalide, or 6-X-3-(4'-naphthal-1')phthalide (0.01 mole) and potassium bichromate (7 g) in concentrated acetic acid (100 ml) was stepwise treated with concentrated sulfuric acid (10 ml). The mixture was heated until the liquid turns green (15—20 minutes). The hot solution was then filtered off and the filtrate was diluted with water. The precipitate was separated and dissolved in an aqueous sodium hydrogen carbonate solution. Upon acidulation the proper 4-Y-naphthoic acid precipitates. 4-Chloronaphthoic acid crystallized from ethanol forms whitish needles, m.p. 209°C (cf. [9] 210°C).

For $C_{11}H_7O_2Cl$ (206.62) calculated: 17.16% Cl; found: 17.32%Cl.

4-Bromonaphthoic acid crystallized from chloroform forms white needles, m.p. 218—219°C (cf. [9] 220°C).

For $C_{11}H_7O_2Br$ (251.1) calculated: 31.83% Br; found: 31.96%Br.

4-Nitronaphthoic acid crystallized from diluted ethanol (1 : 1) forms yellow needles, m.p. 221°C in accordance with the reported m.p. [9].

For $C_{11}H_7O_4N$ (217.2) calculated: 6.45% N; found 6.83% N.

Yields, melting points and elemental analyses are listed in Table 1.

Yields of substances *Ia*, *Ib*, *IIa*, *IIb*, *IIIa*, *IIIb* resulted from chromatographic separation.

Infra-red spectra were taken with a UR-20 apparatus (Carl Zeiss, Jena) in 0.2 M chloroform solution. (Calibration with polystyrene foil.)

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