Perkin Synthesis of Bromobenzalphthalides. Their Reactions with Amines and Hydrazine

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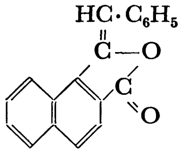
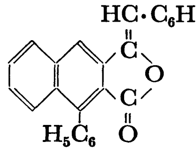
The isomeric 5-bromo- and 6-bromo-3-benzalphthalides were prepared by condensation of 4-bromophthalic anhydride with phenylacetic acids. The reaction of such isomeric bromobenzalphthalides with primary aromatic amines give the corresponding bromobenzalphthalimidines. Bromophthalazinone derivatives were obtained in good yields by the reatcion of bromobenzalphthalides with hydrazine hydrate.

It has been reported[1-4] that symmetric anhydrides react with phenylacetic acids in the presence of sodium or potassium acetate to give the corresponding monobenzal derivatives. The interaction of asymmetric anhydrides with phenylacetic acids in the Perkin reaction should lead to the formation of structural isomers.

The condensation of naphthalene-1,2-dicarboxylic[2] and 1-phenylnaphthalene-2,3-dicarboxylic anhydrides[3-4] with phenylacetic acid was reported to give only one isomer (I and II).

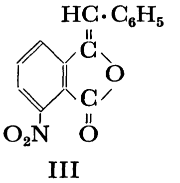


I



II

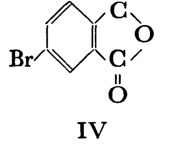
On the other hand, there are a few instances which report the isolation of two structural isomers from a Perkin condensation of phenylacetic acid with 3-nitrophthalic[5] and 4-nitrophthalic anhydrides,[6-7] though Zelmens and Vanages[8] isolated only one isomer (III) in the former case.



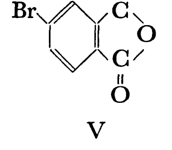
III

Recently, however, Islam[9] found that the condensation of 3-nitrophthalic anhydride with phenylacetic acid gives actually a mixture of the two structural isomers 4-nitro- and 7-nitro-3-benzalphthalides.

In the present investigation, we report that the condensation of 4-bromophthalic anhydride with phenylacetic or *p*-nitrophenylacetic acid gave isomeric bromobenzalphthalides (IVa—b) and (Va—b).



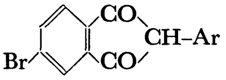
IV



V

a: Ar=C_6H_5; b: Ar=$C_6H_4 \cdot NO_2$-*p*

These products (IV—V) showed stretching frequency at 1780 cm^{-1} characteristic for benzalphthalides.[10] The isomeric nature of these products was proved unequivocally by the fact that both (IVa) and (Va) were readily rearranged under the influence of sodium methoxide, to 5-bromo-2-phenylindan-1,3-dione (VIa). Similarly, both (IVb) and (Vb) were rearranged to 5-bromo-2-(*p*-nitrophenyl)indan-1,3-dione (VIb).



VI

a: Ar=C_6H_5; b: Ar=$C_6H_4 \cdot NO_2$-*p*

The compounds (VI) showed stretching frequency at 1690—1655 cm^{-1} characteristic for the 1,3-dione group.[10]

Unequivocal chemical evidence for these structural isomers IVa, IVb, Va, and Vb was achieved by the direct synthesis of particular isomers.

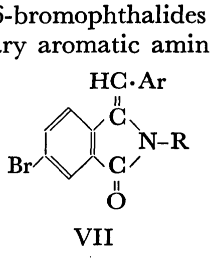
Condensation of 6-bromophthalide with benzaldehyde in the presence of catalytic amounts of piperidine gave a product, mp 139 °C, identical with the product IVa. On this basis, the isomer IVa was identified as 3-benzal-6-bromophthalide, while the second isomer of high melting point 180 °C was tentatively given structure Va as 3-benzal-5-bromophthalide.

Similarly, condensation of 6-bromophthalide with *p*-nitrobenzaldehyde gave a product, mp 160 °C, identical with (IVb). The high melting isomer (mp 220 °C) was tentatively given structure (Vb).

It is worth to note that in this series, the benzalphthalides substituted at position 6 always possess lower melting points than the corresponding 5-substituted analogues.

In agreement with the previous work,[11] reaction of bromobenzalphthalides (IV) and (V) with amines gave the corresponding bromobenzalphthalimidines.

Thus, 3-benzal-6-bromophthalides (IVa—b) reacted readily with primary aromatic amines such as aniline,

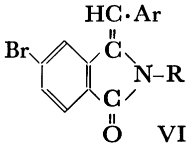


VII

a: Ar=C_6H_5; R=C_6H_5
b: Ar=C_6H_5; R=$C_6H_4 \cdot CH_3$-*o*
c: Ar=C_6H_5; R=$C_6H_4 \cdot CH_3$-*m*
d: Ar=C_6H_5; R=$C_6H_4 \cdot CH_3$-*p*
e: Ar=C_6H_5; R=$C_6H_4 \cdot NO_2$-*p*
f: Ar=$C_6H_4 \cdot NO_2$-*p*; R=C_6H_5

o-toluidine, *m*-toluidine, *p*-toluidine, and *p*-nitroaniline to give the corresponding 2-aryl-3-benzal-6-bromophthalimidines (VIIa—f).

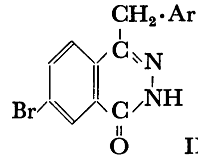
Similarly 3-benzal-5-bromophthalides (Va—b) reacted with the same amines to give the corresponding 2-aryl-3-benzal-5-bromophthalimidines (VIIIa—h).



VIII

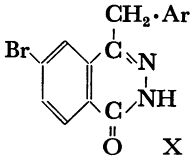
a: Ar=C_6H_5;	R=C_6H_5
b: Ar=C_6H_5;	R=$C_6H_4\cdot CH_3$-*o*
c: Ar=C_6H_5;	R=$C_6H_4\cdot CH_3$-*m*
d: Ar=C_6H_5;	R=$C_6H_4\cdot CH_3$-*p*
e: Ar=C_6H_5:	R=$C_6H_4\cdot NO_2$-*p*
f: Ar=$C_6H_4\cdot NO_2$-*p*;	R=C_6H_5
g: Ar=$C_6H_4\cdot NO_2$-*p*;	R=$C_6H_4\cdot CH_3$-*p*
h: Ar=$C_6H_4\cdot NO_2$-*p*;	R=$C_6H_4\cdot NO_2$-*p*

In agreement with the finding of Ephraim[12] and Islam,[9] the isomeric bromobenzalphthalides (IV, V) reacted readily with hydrazine hydrate in alcohol solution to give 4-arylmethyl-7-bromophthalazin-1-ones (IXa—b) and 4-arylmethyl-6-bromophthalazin-1-ones (Xa—b).



IX

a: Ar=C_6H_5
b: Ar=$C_6H_4\cdot NO_2$-*p*



X

a: Ar=C_6H_5
b: Ar=$C_6H_4\cdot NO_2$-*p*

Experimental

Analytical data were determined in the microanalytical unit at Cairo University, Infra-red spectra were recorded on SP 1200 a Pye-Unicam Spectrophotometer. Melting points are uncorrected.

Condensation of 4-Bromophthalic Anhydride with Phenylacetic Acid. A mixture of 4-bromophthalic anhydride (22.7 g), phenylacetic acid (13.6 g) and freshly fused sodium acetate (2.0 g) was fused together at 180—200 °C for one hour. The cold reaction mass was washed with dilute sodium carbonate solution (100 ml) to remove unreacted materials. The remaining solid (15 g, 50%) was extracted with boiling ethanol (100 ml), which on crystallization gave 3-benzal-6-bromophthalide (IVa) (9.0 g, 30%) as yellow powder, mp 139—141 °C. Found: C, 60.26; H, 3.38; Br, 27.0%. Calcd for $C_{15}H_9O_2Br$: C, 59.80; H, 3.00; Br, 26.58%.

The alcohol-insoluble residue was recrystallized from acetic acid to give 3-benzal-5-bromophthalide (Va), (4.5 g, 15%) as pale yellow crystals, mp 180—182 °C. Found: C, 59.67; H, 3.22; Br, 26.9%. Calcd for $C_{15}H_9O_2Br$: C, 59.80; H, 3.00; Br, 26.58%.

5-Bromo-2-phenylindan-1,3-dione (VIa). A solution of (IVa) (3 g) in methanol (80 ml) was treated with sodium methoxide solution (100 ml) and the mixture was heated under reflux for 1 hr. The cold mixture was diluted with water and acidified with cold dilute sulphuric acid. Recrystallization of the obtained brown solid from methanol gave (VIa) (1.4 g, 46.4%) as reddish-brown prisms, mp 164—165 °C. Found: C, 60.15; H, 3.44%. Calcd for $C_{15}H_9O_2Br$: C, 59.80; H, 3.00%.

Similarly, (Va) (3 g) gave the same product (VIa) (1.2 g, 40%).

Condensation of 4-Bromophthalic Anhydride with p-*Nitrophenyl-*

Table 1. Reaction of bromobenzalphthalides with amines

Bromobenzal-phthalide	Amine	Product	Solv. of crystn.	Colour	Mp (°C)	Yield (%)	Analysis %: Calcd Found C	H	N
IVa	Aniline	VIIa	AcOH	Creamy	188	65	67.02	3.72	3.72
							67.23	3.65	3.32
IVa	*o*-Toluidine	VIIb	EtOH	Colourless	167	92	67.69	4.10	3.58
							66.54	4.03	3.12
IVa	*m*-Toluidine	VIIc	AcOH	White	175	72	67.69	4.10	3.58
							67.28	3.82	3.43
IVa	*p*-Toluidine	VIId	EtOH	Pale yellow	149	82	67.69	4.10	3.58
							66.94	4.62	3.42
IVa	*p*-Nitroaniline	VIIe	AcOH	Yellow	195	66	59.85	3.08	6.65
							59.32	2.94	6.55
IVb	Aniline	VIIf	AcOH	Yellow	184	63	59.85	3.08	6.65
							59.63	3.11	6.30
IVa	Aniline	VIIIa	AcOH	White	192	59	67.02	3.72	3.72
							67.08	3.63	3.43
IVa	*o*-Toluidine	VIIIb	EtOH	Colourless	198	92	67.69	4.10	3.58
							66.99	3.92	3.33
Va	*m*-Toluidine	VIIIc	AcOH	White	205	82	67.69	4.10	3.58
							67.41	3.71	3.35
Va	*p*-Toluidine	VIIId	EtOH	Cream	176	77	67.69	4.10	3.58
							67.04	3.63	3.64
Va	*p*-Nitroaniline	VIIIe	AcOH	Pale yellow	212	74	59.85	3.08	6.65
							59.08	3.12	6.86
Va	Aniline	VIIIf	EtOH	Yellow	224	76	59.85	3.08	6.65
							59.71	2.88	6.55
Vb	*p*-Toluidine	VIIIg	EtOH	Yellow orange	241	69	60.68	3.44	6.43
							60.51	3.30	6.86
Vb	*p*-Nitroaniline	VIIIh	AcOH	Yellow	205	76	54.07	2.57	9.01
							54.00	2.41	8.78

acetic Acid. A mixture of 4-bromophthalic anhydride (22.7 g), *p*-nitrophenylacetic acid (18.1 g) and freshly fused sodium acetate (2 g) was fused together at 220—240 °C for one hour. The cold mass was washed with dilute sodium carbonate solution, boiled with acetic acid, and cooled. The insoluble part was recrystallized from acetic acid to give 5-bromo-3-(*p*-nitrobenzal)-phthalide (Vb) (8.1 g, 23%) as yellow crystals, mp 219—221 °C. Found: C, 51.94; H, 2.19; N, 3.92%. Calcd for $C_{15}H_8NO_4Br$: C, 52.02; H, 2.31; N, 4.04%.

The mother-liquor gave, on concentration and addition of ethanol, a dark yellow solid which was recrystallized from dilute acetic acid to give 3-(*p*-nitrobenzal)-6-bromophthalide (IVb) (2.7 g, 8%) as yellow crystals, mp 159—161 °C. Found: C, 51.87; H, 2.41; N, 4.23%. Calcd for $C_{15}H_8NO_4Br$: C, 52.02; H, 2.31; N, 4.04%.

*5-Bromo-2-(*p*-nitrophenyl)-indan-1,3-dione (VIb).* A mixture of (IVb) (3.4 g) and methanol (100 ml) was heated with sodium methoxide solution (100 ml) under reflux for one hour. The cold reaction mixture was diluted with water (100 ml) and acidified with cold dilute sulphuric acid. Recrystallization of the reddish brown solid obtained from acetic acid gave (VIb) (2.1 g, 63%) as reddish brown needles, mp 199—200 °C. Found: C, 51.73; H, 1.98; N, 4.12%. Calcd for $C_{15}H_8NO_4Br$: C, 52.02; H, 2.31; N, 4.04%.

Similarly, (Vb) (3.4 g) gave the same compound (VIb) (1.9 g, 65%), mp 199—200 °C.

3-Benzal-6-bromophthalide (IVa). A mixture of 6-bromo phthalide (2.2 g), benzaldehyde (1 g) and 3 drops of piperidine was fused at 220—240 °C for 3 hr. After being cooled, the obtained solid was recrystallized from ethanol to give (IVa), mp 139—141 °C (1.4 g, 47%) as yellow crystals. The melting point did not depress when mixed with a sample of (IVa) obtained from 4-bromophthalic anhydride.

*3-(*p*-Nitrobenzal)-6-bromophthalide (IVb).* A mixture of 6-bromophthalide (2.2 g), *p*-nitrobenzaldehyde (1.5 g) was treated similarly. The obtained solid was recrystallized from acetic acid to give (IVb) (2.1 g, 61%) as pale yellow crystals, mp 159—161 °C. The melting point did not depress when mixed with a sample of (IVb) obtained from 4-bromophthalic anhydride.

Bromobenzalphthalimidine (VII—VIII). A mixture of the bromobenzalphthalides (0.1 mol) and appropriate amine (0.12 mol) in acetic acid (30 ml) containing freshly fused sodium acetate (0.1 g) was heated under reflux for 36 hr. The reaction mixture was decomposed with dilute hydrochloric acid. Recrystallization of the product gave the corresponding bromobenzalphthalimidines (*cf.* Table 1).

Table 2. Reaction of bromobenzalphthalides with hydrazine

Bromobenzal-phthalide	Product	Mp (°C)	Yield (%)	Analysis %: Calcd Found		
				C	H	N
IVa	IXa	175—177	66	57.14	3.49	8.88
				57.01	3.32	8.90
IVb	IXb	175—177	55	50.00	2.77	11.66
				49.72	2.61	11.91
Va	Xa	196—198	79	57.14	3.49	8.88
				57.11	3.22	8.71
Vb	Xb	235—236	77	50.00	2.77	11.66
				49.91	2.53	12.01

Bromophthalazones (IX—X). A mixture of bromobenzalphthalides (0.1 mol) and hydrazine hydrate (3 ml, excess) in ethanol (30 ml) was heated under reflux for 20 min. The cold solution was diluted with water (70 ml). Recrystallization of the obtained solid from ethanol gave the corresponding bromophthalazones as colourless crystals (*cf.* Table 2).

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