

On phthalides and 1,3-indandiones. LIII.*
Phthalides and 1,3-indandiones from (arylthio)acetic
and aryloxyacetic acids

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3-Aryloxymethylenephthalides and 3-arylthiomethylenephthalides were prepared from phthalic anhydride and aryloxy- or (arylthio)acetic acids by the Gabriel modification of the Perkin synthesis [1]. Rearrangement of these phthalides led to 2-arylthio-1,3-indandiones and to 2-aryloxy-1,3-indandiones, which afforded bis(2-aryloxy-1,3-indandiones).

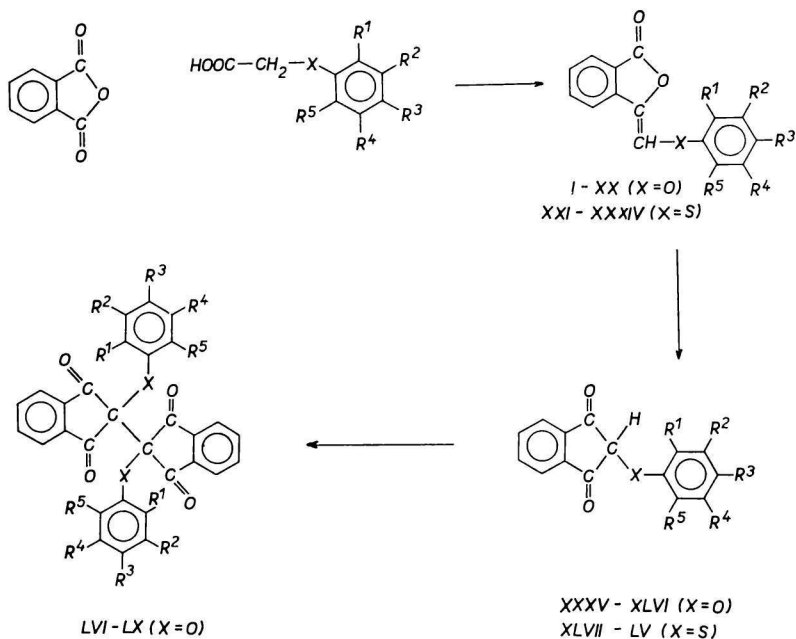
So far, little attention has been paid to the Gabriel modification of the Perkin synthesis of phthalides and 1,3-indandiones from (arylthio)acetic acids; this contribution extends our previous papers [2, 3].

The goal of this study was to examine the possible herbicidal (aryloxyacetic and in lesser extent also (arylthio)acetic acids were reported to be significant herbicides) and hypotrombinemic activity [4]. These substances are also potential starting materials for further syntheses.

Phthalic anhydride when reacting with aryloxyacetic or (arylthio)acetic acids according to Scheme 1 afforded 3-aryloxymethylenephthalides (*I-XX*) or 3-arylthiomethylenephthalides (*XXI-XXXIV*). The rearrangement of phthalides (*I-XX*) in sodium methoxide led to 2-aryloxy-1,3-indandiones (*XXXV-XLVI*), which gave bis(2-aryloxy-1,3-indandiones) (*XLVI-LX*). Phthalides *XXI-XXXIV* rearranged to 2-arylthio-1,3-indandiones (*XLVII-LV*).

When contrasting yields of phthalides from arylacetic acids with those from aryloxy- and (arylthio)acetic acids, it becomes evident that the best yields were found with arylacetic acids which gave, in 60% yield, preferentially *trans* isomers of benzalphthalides (the *trans* to *cis* ratio 100 : 1) [5, 6]. Under optimal conditions (200–220°C, reaction time 3–4 hours) the yields of phthalides from (arylthio)acetic acids were about 50% (*trans* to *cis* isomer ratio was estimated to be 9 : 1) and from aryloxyacetic acids about 30% at 220–230°C (*cis* to *trans* isomer ratio was approximately 2 : 1). 3-Aryloxymethylenephthalides (*I-XX*) are under the temperature conditions of the reaction unstable and after a certain period of time (50 or more minutes depending on the nature of the substituent) they underwent decomposition and turned brown. The best reaction time was found to be 150–180 minutes.

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R^1-R^5 = hydrogen, halogen, NO_2 , NH_2 , alkyl, aryl, or their combinations.

Scheme 1

The different solubility in organic solvents was utilized to separate the geometric isomers ($I-XXI$), which were characterized by melting points, spectral methods [7], and gas chromatography [3]. Both isomers were converted into 2-aryloxy-1,3-indandione as a sole product. In ethanol better soluble isomers assumed to have the *cis* configuration, having lower melting points and a lower $C=O$ stretching frequency (prepared usually also in lower yields), rearrange into *trans* isomers of higher melting points. The shift of the carbonyl band in the i.r. spectra is substituent R dependent. A linear relation of those shifts with σ constants has been observed; both isomers differ in the slope [7]. From among the sulfur analogs we succeeded to isolate only the *cis*-3-phenylthiomethylenephthalide (XXI).

It has been found that nitrophenoxyacetic acids give the corresponding phthalides in very low yields and therefore, it is convenient to synthesize them according to [8]. Compounds $XVI-XVIII$ and XXX having a nitro group could be reduced with zinc in acetic acid to yield amino derivatives, which gave, by diazotization and Sandmeyer reaction, products $XXIX$ and $XXXI-XXXIV$.

Whereas the rearrangement of sulfur analogs of phthalides is almost quantitative, that of oxygen derivatives varies between 40–50%. Indandiones $XLVII-LV$ are more stable than the oxygen analogs thereof which, either during crystallization or when allowed to stand, gave bis(2-aryloxy-1,3-indandione) in about 30% yield, this being further decomposed to furnish the corresponding substituted phenol. The yield of indandiones $LVI-LX$ could be raised by heating the solutions, or by addition of hydrogen peroxide at $100^\circ C$. It is noteworthy that substituents revealing the +I effect

Table I
Characteristic data of 3-aryloxymethylenephthalides (I—XX)

Compound	R ¹	R ²	R ³	R ⁴	Formula	M	Calculated/found		Yield [%]	M.p. [°C]
							% C	% H		
<i>I cis</i>	CH ₃	H	H	H	C ₁₆ H ₁₂ O ₃	252.27	76.17 75.84	4.97 4.50	8.7	104—105
<i>I trans</i>	CH ₃	H	H	H	C ₁₆ H ₁₂ O ₃	252.27	76.17 76.20	4.97 4.46	20.0	170—171
<i>II cis</i>	H	CH ₃	H	H	C ₁₆ H ₁₂ O ₃	252.27	76.17 76.38	4.79 4.58	12.6	77—78
<i>II trans</i>	H	CH ₃	H	H	C ₁₆ H ₁₂ O ₃	252.27	76.17 76.01	4.79 4.90	21.5	146—147
<i>III cis</i>	H	H	CH ₃	H	C ₁₆ H ₁₂ O ₃	252.27	76.17 76.31	4.79 4.62	9.3	89—91
<i>III trans</i>	H	H	CH ₃	H	C ₁₆ H ₁₂ O ₃	252.27	76.17 76.18	4.79 4.83	29.7	148—150
<i>IV</i>	H	CH ₃	CH ₃	H	C ₁₇ H ₁₄ O ₃	266.29	76.67 76.59	5.29 4.93	8.0	164
<i>IV trans</i>	H	CH ₃	CH ₃	H	C ₁₇ H ₁₄ O ₃	266.29	76.67 76.71	5.29 5.08	18.6	193
<i>V cis</i>	H	C ₂ H ₅	H	H	C ₁₇ H ₁₄ O ₃	266.29	76.67 76.52	5.29 5.30	8	40
<i>V trans</i>	H	C ₂ H ₅	H	H	C ₁₇ H ₁₄ O ₃	266.29	76.67 76.48	5.29 5.08	17	102
<i>VI cis</i>	Cl	H	H	H	C ₁₅ H ₉ O ₃ Cl	272.69	66.06 66.23	3.32 3.54	9.5	124
<i>VI trans</i>	Cl	H	H	H	C ₁₅ H ₉ O ₃ Cl	272.69	66.06 66.35	3.32 3.28	19.2	148—149
<i>VII cis</i>	H	Cl	H	H	C ₁₅ H ₉ O ₃ Cl	272.69	66.06 62.28	3.32 3.11	12	128—130

Table 1 (Continued)

Compound	R ¹	R ²	R ³	R ⁴	Formula	M	Calculated/found		Yield [%]	M.p. [°C]
							% C	% H		
<i>VII trans</i>	H	Cl	H	H	C ₁₅ H ₉ O ₃ Cl	272.69	66.06 66.35	3.32 3.05	23	168
<i>VIII cis</i>	H	H	Cl	H	C ₁₅ H ₉ O ₃ Cl	272.69	66.06 65.88	3.32 3.48	10.1	156—157
<i>VIII trans</i>	H	H	Cl	H	C ₁₅ H ₉ O ₃ Cl	272.69	66.06 65.92	3.32 3.48	19.8	177—178
<i>IX cis</i>	Cl	H	Cl	H	C ₁₅ H ₈ O ₃ Cl ₂	307.14	58.65 58.42	2.62 2.47	7.1	135—136
<i>IX trans</i>	Cl	H	Cl	H	C ₁₅ H ₈ O ₃ Cl ₂	307.14	58.65 58.90	2.62 2.80	17.9	220—221
<i>X cis</i>	Cl	H	Cl	Cl	C ₁₅ H ₇ O ₃ Cl ₃	314.59	52.74 53.08	2.06 2.18	8.9	215—216
<i>X trans</i>	Cl	H	Cl	Cl	C ₁₅ H ₇ O ₃ Cl ₃	314.59	52.74 52.92	2.06 2.18	18.7	266—268
<i>XI cis</i>	CH ₃	H	Cl	H	C ₁₆ H ₁₁ O ₃ Cl	286.72	67.02 67.07	3.86 4.01	10.8	128—129
<i>XI trans</i>	CH ₃	H	Cl	H	C ₁₆ H ₁₁ O ₃ Cl	286.72	67.02 66.83	3.86 4.11	26.8	198
<i>XII cis</i>	H	CH ₃	Cl	H	C ₁₆ H ₁₁ O ₃ Cl	286.72	67.02 67.21	3.86 4.05	11.6	83—84
<i>XII trans</i>	H	CH ₃	Cl	H	C ₁₆ H ₁₁ O ₃ Cl	286.72	67.02 67.12	3.86 3.96	30.5	168—169
<i>XIII trans</i>	H	F	H	H	C ₁₆ H ₉ O ₃ F	256.27	70.31 70.20	3.54 3.63	19	161.5
<i>XIV cis</i>	H	H	F	H	C ₁₅ H ₉ O ₃ F	256.27	70.31 70.39	3.54 3.96	13	135

Table 1 (Continued)

Compound	R ¹	R ²	R ³	R ⁴	Formula	M	Calculated/found		Yield [%]	M.p. [°C]
							% C	% H		
<i>XIV trans</i>	H	H	F	H	C ₁₅ H ₉ O ₃ F	256.27	70.31 70.50	3.54 3.66	25	195—196
<i>XV cis</i>	H	H	I	H	C ₁₅ H ₉ O ₃ I	364.18	49.46 49.23	2.49 2.38	10	156
<i>XV trans</i>	H	H	I	H	C ₁₅ H ₉ O ₃ I	364.18	49.46 49.69	2.49 2.12	16	208—209
<i>XVI cis</i>	NO ₂	H	H	H	C ₁₅ H ₉ O ₅ N	283.28	63.60 63.71	3.20 3.15	5	187—188
<i>XVI trans</i>	NO ₂	H	H	H	C ₁₅ H ₉ O ₅ N	283.28	63.60 63.41	3.20 3.45	8.5	213—214
<i>XVII cis</i>	H	NO ₂	H	H	C ₁₅ H ₉ O ₅ N	283.21	63.60 63.92	3.20 3.35	6	168
<i>XVII trans</i>	H	NO ₂	H	H	C ₁₅ H ₉ O ₅ N	283.28	63.60 63.29	3.20 3.61	11	261
<i>XVIII cis</i>	H	H	NO ₂	H	C ₁₅ H ₉ O ₅ N	283.28	63.60 63.30	3.20 3.56	5	189—190
<i>XVIII trans</i>	H	H	NO ₂	H	C ₁₅ H ₉ O ₅ N	283.28	63.60 63.56	3.20 3.52	9	288—289
<i>XIX cis</i>	H	H	C ₆ H ₅	H	C ₂₁ H ₁₄ O ₃	314.34	80.23 80.46	4.49 4.43	9.4	154.5
<i>XIX trans</i>	H	H	C ₆ H ₅	H	C ₂₁ H ₁₄ O ₃	314.34	80.23 80.11	4.49 4.72	25.0	187.5
<i>XX cis</i>	<i>n</i> -C ₃ H ₇	H	H	CH ₃	C ₁₉ H ₁₈ O ₃	294.25	77.52 77.61	6.16 6.17	7.9	101—102
<i>XX tr</i>	<i>i</i> -C ₃ H ₇	H	H	CH ₃	C ₁₉ H ₁₈ O ₃	294.25	77.52 77.40	6.16 6.27	11.5	152—154

Table 2

Characteristic data of 3-arylthiomethylenephthalides (XXI—XXXIV)

Compound	R ¹	R ²	R ³	R ⁴	R ⁵	Formula	M	Calculated/found			Yield [%]	M.p. [°C]
								% C	% H	% S		
XXI <i>trans</i>	H	H	H	H	H	C ₁₅ H ₁₀ O ₂ S	244.50	70.84	3.96	12.61	50	148—149
								71.03	3.58	12.32		
XXI <i>cis</i>	H	H	H	H	H	C ₁₅ H ₁₀ O ₂ S	244.30	70.84	3.96	12.61	5	120—122
								70.92	3.61	12.22		
XXII	CH ₃	H	H	H	H	C ₁₆ H ₁₂ O ₂ S	268.32	71.61	4.50	11.95	53	143—144
								71.84	4.63	11.82		
XXIII	H	H	CH ₃	H	H	C ₁₆ H ₁₂ O ₂ S	268.32	71.61	4.50	11.95	50	147—148
								71.65	4.38	11.67		
XXIV	H	H	Cl	H	H	C ₁₅ H ₉ O ₂ ClS	288.76	62.39	3.14	11.10	60	173—175
								62.46	3.28	11.34		
XXV	H	Cl	H	H	H	C ₁₅ H ₉ O ₂ ClS	288.76	62.39	3.14	11.10	60	126
								62.21	3.04	11.19		
XXVI	Cl	H	H	Cl	H	C ₁₅ H ₈ O ₂ Cl ₂ S	323.19	55.73	2.48	9.92	63	178—179
								55.98	2.13	9.49		
XXVII	Cl	Cl	Cl	Cl	Cl	C ₁₅ H ₆ O ₂ Cl ₅ S	426.55	42.24	1.18	7.52	61	244—246
								42.01	1.41	7.25		
XXVIII	H	H	Br	H	H	C ₁₅ H ₉ O ₂ BrS	333.22	54.06	2.72	9.62	63	194—196
								53.81	2.43	9.68		
XXIX	H	H	I	H	H	C ₁₅ H ₉ O ₂ IS	380.21	47.38	2.38	33.38	31	154—155
								47.54	2.29	33.30		
XXX	H	H	NO ₂	H	H	C ₁₅ H ₉ O ₁ NS	299.32	60.17	3.03	10.71	45	228—230
								60.22	3.12	10.58		
XXXI	H	H	OH	H	H	C ₁₅ H ₁₀ O ₃ S	270.31	66.64	3.72	11.86	28	170
								66.92	3.51	11.76		
XXXII	H	H	CH ₃ CONH	H	H	C ₁₇ H ₁₃ O ₃ SN	311.35	65.57	4.20	10.29		116—117
								65.34	4.24	10.48		
XXXIII	H	NO ₂	H	H	H	C ₁₅ H ₉ O ₄ NS	299.32	60.17	3.03	10.71	50	168
								60.38	3.19	10.96		
XXXIV	H	NH ₂	H	H	H	C ₁₅ H ₁₁ O ₂ NS	269.28	66.81	4.11	11.96	40	148
								66.58	4.28	11.54		

Table 3
Characteristic data of 2-aryloxy-1,3-indandiones (XXXV—XLVI)

Compound	R ¹	R ²	R ³	R ⁴	Formula	M	Calculated/found		Yield [%]	M.p. [°C]
							% C	% H		
XXXV	CH ₃	H	H	H	C ₁₆ H ₁₂ O ₃	252.27	76.17 76.36	4.79 4.80	68	144.5
XXXVI	H	CH ₃	H	H	C ₁₆ H ₁₂ O ₃	.27	76.17 76.41	4.79 4.72	67	59.5—61
XXXVII	H	H	CH ₃	H	C ₁₆ H ₁₂ O ₃		76.17 76.21	4.79 4.98	61	70—72
XXXVIII	H	CH ₃	CH ₃	H	C ₁₇ H ₁₄ O ₃	266.29	76.67 76.61	5.29 5.30	80	125
XXXIX	Cl	H	H	H	C ₁₅ H ₉ O ₃ Cl	272.69	66.06 66.29	3.32 3.50	52	163—164
XL	H	H	Cl	H	C ₁₅ H ₉ O ₃ Cl	272.69	66.06 66.28	3.32 3.15	56	191—192
XLI	Cl	H	Cl	H	C ₁₅ H ₈ O ₃ Cl ₂	307.14	58.65 58.41	2.62 2.84	51	162—163
XLII	Cl	H	Cl	Cl	C ₁₅ H ₇ O ₃ Cl ₃	314.59	52.74 52.96	2.06 2.24	53	149—150
XLIII	CH ₃	H	Cl	H	C ₁₆ H ₁₁ O ₃ Cl	286.72	67.02 67.01	3.86 3.89	62	156—157
XLIV	H	CH ₃	Cl	H	C ₁₆ H ₁₁ O ₃ Cl	286.72	67.02 67.09	3.86 4.02	62	178—179
XLV	H	H	C ₆ H ₅	H	C ₂₁ H ₁₄ O ₃	314.34	80.23 80.50	4.49 4.60	58	173—175
XLVI	-C ₃ H ₇	H	H	CH ₃	C ₁₉ H ₁₈ O ₃	294.25	77.52 77.76	6.16 5.82	81	87

Table 4
 Characteristic data of 2-arylthio-1,3-indandiones (*XLVII—LV*)

Compound	R ¹	R ²	R ³	R ⁴	R ⁵	Formula	M	Calculated/found			M.p. [°C]
								% C	% H	% S	
<i>XLVII</i>	H	H	H	H	H	C ₁₅ H ₁₀ O ₂ S	244.30	70.84 70.84	3.96 3.66	12.61 12.28	90—92
<i>XLVIII</i>	CH ₃	H	H	H	H	C ₁₆ H ₁₂ O ₂ S	268.32	71.61 71.85	4.50 4.48	11.95 11.68	145—146
<i>XLIX</i>	H	H	CH ₃	H	H	C ₁₆ H ₁₂ O ₂ S	268.32	71.61 71.88	4.50 4.61	11.95 11.98	142—143
<i>L</i>	H	H	Cl	H	H	C ₁₅ H ₉ O ₂ ClS	288.76	62.39 62.59	3.14 3.29	11.10 11.40	113
<i>LI</i>	H	H	Br	H	H	C ₁₅ H ₉ O ₂ BrS	333.22	54.06 54.10	2.72 2.58	9.62 9.36	150—151
<i>LII</i>	Cl	H	H	Cl	H	C ₁₅ H ₈ O ₂ Cl ₂ S	323.19	53.73 55.80	2.48 2.50	9.92 10.01	138—139
<i>LIII</i>	Cl	Cl	Cl	Cl	Cl	C ₁₅ H ₅ O ₂ Cl ₅ S	426.55	42.24 41.90	2.48 2.11	7.52 7.33	231 deccmp.
<i>LIV</i>	H	NO ₂	H	H	H	C ₁₅ H ₉ O ₄ NS	299.32	60.17 60.16	3.03 3.17	10.71 10.86	138
<i>LV</i>	H	H	NO ₂	H	H	C ₁₅ H ₉ O ₄ NS	299.32	60.17 60.32	3.03 3.32	10.71 10.89	160—162

Table 5
Characteristic data of bis (2-aryloxy-1,3-indandiones) (LVI—LX)

Compound	Aryl	Formula	<i>M</i>	Calculated/found		Yield [%]	M.p. [°C]	$\bar{\nu}(\text{C}=\text{O})$ [cm ⁻¹]
				% C	% H			
LVI	Phenyl	C ₃₀ H ₁₈ O ₆	474.44	75.94 76.06	3.82 4.16	34	291	1731 s 1748 m
LVII	3-Methylphenyl	C ₃₂ H ₂₂ O ₆	502.49	76.42 76.28	4.41 4.28	38	266.5	1728 s 1746 m
LVIII	4-Methylphenyl	C ₃₂ H ₂₂ O ₆	502.49	76.42 76.42	4.41 4.68	40	287—288	1730 s 1747 m
LIX	2,5-Dimethylphenyl	C ₃₄ H ₂₆ O ₆	530.57	76.94 76.66	4.84 4.80	72	274	1734 s
LX	β -Naphthyl	C ₃₈ H ₂₂ O ₆	574.55	79.43 79.72	3.85 3.81	46	264—265	1732 s 1747 m

s — strong; m — medium,

stimulate the formation of bis derivatives, which have not been hitherto prepared. There are oxidation reactions leading to bis(2-aryl-1,3-indandiones) [9–11]; nevertheless no spontaneous formation of those substances at room temperature was reported. Infra-red spectra [7], p.m.r. spectrometry [12], and polarography [13, 14] were the tools we used to investigate the phthalides in more detail.

Several substances (*I–XX*) were found to possess a herbicidal activity [15], other (*XXI–LV*) are much less effective [16]. Compounds *IV*, *X–XII*, *XVI*, *XVIII*, *XXI*, *XXVI*, *XLIII*, *XLIV*, *XLVII*, and *LII* were tested to inhibit the bacteriostatic and fungistatic activity. No inhibition of growth up to 500 µg/1 ml was observed with *Escherichia coli*, *Salmonella typhi murium*, *Staphylococcus pyogenes aureus*, *Candida albicans*, *Trichophyton rubrum*, *Trichophyton flaviformae*, *Trichophyton violaceum*, *Trichophyton gypsum*, *Trichophyton Kaufman Wolf*, *Microsporum gypsum*, and *Microsporum cookei*.

Experimental

Infrared spectra were measured with a UR-20 Zeiss spectrophotometer in nujol mull. 3-Aryloxymethylenephthalides (*I–XX*) and 3-arylthiomethylenephthalides (*XXI–XXXIV*) were prepared according to [1–3, 15], 2-aryloxy-1,3-indandiones (*XXXV–XLVI*) and 2-arylthio-1,3-indandiones (*XLVII–LV*) according to [2, 3].

Bis(2-aryloxy-1,3-indandiones) (LVI–LX)

2-Aryloxy-1,3-indandione (4.2 mmoles) was refluxed 10 hours at 110°C. The decomposition product was allowed to cool, then diluted with diethyl ether and filtered. The crystalline residue was washed with the same solvent until it was yellow, and then it was crystallized from dimethylformamide.

Characteristic data of synthesized substances are surveyed in Tables 1–5.

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