Reactions of Methyl Derivatives of 2-Penten-5-olide, 2-Buten-4-olide, and Coumarin with Dicarboxylic Anhydrides and with 3-Formylchromones under the Perkin Synthesis Conditions

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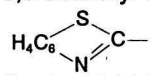
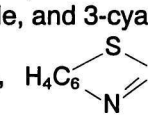
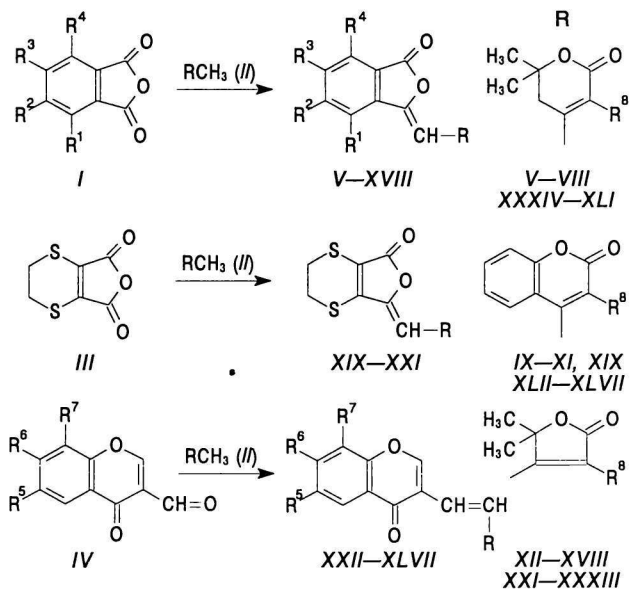
4*H*-4-Oxo-3-(R-vinylene)chromene derivatives and 3-(R-methylene)phthalide derivatives have been prepared by condensation reactions (R = 2*H*,5*H*-2-oxo-5,5-dimethyl-3-R^5-4-furyl; 2*H*-2-oxo-6,6-dimethyl-3-R^5-5,6-dihydropyran-4-yl; 2*H*-2-oxo-3-R^5-4-chromenyl; R^5 = CN, $CONH_2$, $CO_2C_2H_5$, ). Some of the prepared compounds were tested for a variety of biological activities (for herbicidal, fungicidal, growth-regulating activity, for antifungal activity against human pathogenic dermatophytes and micromycetes, and also for their possible anti-HIV activity).

Among chromones, phthalides, and unsaturated aliphatic lactones there are many compounds with considerable biological effects [1—3]. For example, unsaturated γ-lactones with thiazolyl substituents have been found to stimulate germination, mitotic activity and chromosomal aberrations of root cells [1]. Phthalides are known as inhibitors or stimulators of plant growth [4]. Chromones possess a wide spectrum of biological activities. With regard to these facts it can be prospective to synthesize new compounds from both active components and to investigate their biological activities.

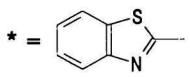
Chromones, phthalides, and unsaturated aliphatic lactones can serve as intermediates for preparation of further groups of compounds.

In this work we have chosen the Perkin synthesis for studying the preparation of compounds *V—XLVII* (Scheme 1). It was confirmed that the methyl groups of the used unsaturated lactones *II* 2-cyano-3,5,5-trimethyl-2-penten-5-olide, 2-R^5-3,4,4-trimethyl-2-buten-4-olide, and 3-cyano-4-methylcoumarin (R^5 = CN, $CO_2C_2H_5$, ) can react as *C*-acids and give with 3-formylchromones and with anhydrides of aromatic dicarboxylic acids aldol condensation products in high yields.

The phthalides *V—XXI* and chromones *XXII—XLVII* with low solubility and high melting points were prepared by two procedures.



	R^1	R^2	R^3	R^4	R^8
V	H	H	H	H	CN
VI	H	COOH	COOH	H	CN
VII	Cl	Cl	Cl	Cl	CN
VIII	H	H	H	H	$CONH_2$
IX	H	COOH	COOH	H	CN
X	Cl	Cl	Cl	Cl	CN
XI	H	H	H	H	CN
XII	H	H	H	H	CN
XIII	Cl	Cl	Cl	Cl	CN
XIV	NO_2	H	H	H	$CONH_2$
XV	H	H	H	H	$CONH_2$
XVI	H	H	H	H	$COOC_2H_5$
XVII	H	H	H	H	*
XVIII	H	COOH	COOH	H	*



	R^5	R^6	R^7	R^8
XXII	H	H	H	CN
XXIII	CH_3	H	H	CN
XXIV	OH	H	H	CN
XXV	Cl	H	H	CN
XXVI	Br	H	H	CN
XXVII	CH_3	CH_3	H	CN
XXIX	CH_3	H	H	$CONH_2$
XXX	OH	H	H	$CONH_2$
XXXI	CH_3	H	H	$COOC_2H_5$
XXXII	OH	H	H	$COOC_2H_5$
XXXIII	CH_3	CH	H	$COOC_2H_5$
XXXIV	H	H	H	CN
XXXV	CH_3	H	H	CN
XXXVI	Cl	H	H	CN
XXXVIII	CH_3	H	H	$CONH_2$
XXXIX	OH	H	H	$CONH_2$
XL	Br	H	H	$CONH_2$
XLI	CH_3	H	Cl	$CONH_2$
XLII	Br	H	H	CN
XLIII	OH	H	H	CN
XLIV	CH_3	CH_3	H	CN
XLV	CH_3	H	Cl	CN
XLVI	CH_3	H	H	$CONH_2$
XLVII	CH_3	H	Cl	$CONH_2$

XIX — 5,6-dihydro-3-(2*H*-2-oxo-3-aminocarbonyl-4-chromenylmethylene)-4,7-dithiaphthalide

XX — 5,6-dihydro-3-(2*H*,5*H*-2-oxo-3-cyano-5,5-dimethyl-4-furylmethylene)-4,7-dithiaphthalide

XXI — 5,6-dihydro-3-(2*H*,5*H*-2-oxo-3-aminocarbonyl-5,5-dimethyl-4-furylmethylene)-4,7-dithiaphthalide

XXVIII — 3-(benzo[*f*]-4*H*-4-oxo-2-chromen-3-ylvinylene)-4,4-dimethyl-2-cyano-2-buten-4-olide

XXXVII — 3-(benzo[*f*]-4*H*-4-oxo-2-chromen-3-ylvinylene)-5,5-dimethyl-2-cyano-2-penten-5-olide

Scheme 1

The aldol condensations of components *I* or *III*, or *IV* with *II* and potassium acetate carried out in acetic anhydride in the temperature range 120—130 °C yielded products with unchanged R^5 groups in high yields (65—75 %). The procedure without acetic anhydride also rendered high yields for phthalides, but higher reaction temperature (150—170 °C) was necessary. Products of chromone with amide group were prepared in toluene at reflux temperature. Under these conditions the nitrile group is partly converted to the amide group by the reaction water. From the crude products both nitriles and amides could be isolated by several crystallizations. The reaction components were decomposed if the reaction was carried out in pyridine at reflux temperature.

The supposed structures of phthalides *V*—*XXI* and chromones *XXII*—*XLVII* were proved by infrared spectra. The C=O stretching frequencies of prepared compounds contained several intensive bands in a wide $\tilde{\nu}$ range of 1640—1805 cm^{-1}. Derivatives of phthalide had two areas of bands, at $\tilde{\nu}$ = 1765—1805 cm^{-1} belonging to carbonyl groups of the phthalide system and $\tilde{\nu}$ = 1730—1760 cm^{-1} belonging to ν(CO) of the group of unsaturated aliphatic lactones. Chromones had also two areas of intensive bands of stretching frequencies of the carbonyl groups. ν(CO) of γ-pyrone appeared in the region of $\tilde{\nu}$ = 1640—1660 cm^{-1} and ν(CO) of unsaturated aliphatic lactone group at $\tilde{\nu}$ = 1705—1730 cm^{-1}.

The condensation products were not sufficiently soluble for measurements of ^1H NMR spectra.

The prepared compounds were tested for herbicidal activity on *Avena sativa*, *Fagopyrum vulgaris*, *Sinapis alba*, *Panicum miliaceum*, and *Lepidium sativum*. The tests showed that the compounds were not phytotoxic even in the maximum dosage of 1.5 g m^{-2} applied.

The phthalides (*V*—*XI*) in standard fungicidal tests on *Erysiphe graminis* showed approximately 25—30 % activity in comparison with that of the standards used. With regard to other tested fungi they were not active.

Chromones *XXII*—*XXXVI* were not active against *Erysiphe graminis*. The tests of 3-formylchromones *III* on *Phytophtora infestans*, *Alternaria species*, *Botrytis cinerea*, and *Fusarium nivale* showed 60 % inhibition of growth, chromones *XXII*—*XXXIV* proved only 30—60 % activity of the reference.

Preliminary biological tests of phthalides *V*—*XI* and of chromones *XXII*—*XXXV* on *Cucumis sativus* showed germination stimulation (11—17 %) and morphological effect similar to that of the phytohormonal compound gibberellin.

At $c = 10^{-7}$ mol dm^{-3} the derivative *X* stimulated the growth and chlorophyll production in *Chlorella vulgaris* by 16 % comparing with that of the control. The inhibition of the algal growth produced by this derivative in $c = 10^{-4}$ mol dm^{-3} was 22 %. In the investigated concentration range the derivative *V* did not affect these processes. From the chromone derivatives only two starting compounds tested for their activity against algae were efficient at $c = 10^{-4}$ mol dm^{-3}, namely 6,8-dichloro- and 6-methyl-8-chloro-3-formylchromone inhibiting the chlorophyll production by about 74 and 68 %, respectively. The inhibition produced by further investigated 3-formylchromones was approximately 12 %. The chlorinated derivatives of 3-formylchromone caused a decrease of the algal growth in the range of 14—40 %.

The chromone derivatives were tested against dermatophytes: *Microsporum gypseum*, *Epidermophyton floccosum*, and *Trichophyton mentagrophytes* var. *interdigitale* and against micromycetes: *Geotrichum candidum* and *Scopulariopsis brevicaulis*. We found that only compounds *XXIII*, *XXV*, *XXVI*, *XXXV*, and *XXXVI* inhibited the growth of *Scopulariopsis brevicaulis* at the mass concentration ρ = 100 mg cm^{-3}. The other compounds were inactive up to ρ = 500 mg cm^{-3}.

Table 1. Characterization of the Prepared Compounds

Compound	Formula M_r	w_i(calc.)/% w_i(found)/%			M.p. °C
		C	H	N	
V	$C_{17}H_{13}NO_4$ 295.2	69.14 68.92	4.45 4.51	4.74 4.62	267—269
VI	$C_{19}H_{13}NO_8$ 383.2	59.51 59.78	3.39 3.52	3.65 3.78	279—280
VII	$C_{17}H_9Cl_4NO_4$ 433.1	47.14 46.85	2.10 2.32	3.24 3.02	240—242
VIII	$C_{17}H_{15}NO_5$ 313.2	65.16 64.88	4.84 4.69	4.47 4.71	247—248
IX	$C_{21}H_7NO_8$ 403.3	62.53 62.45	2.23 2.01	3.47 3.38	360 (decomp.)
X	$C_{19}H_5Cl_4NO_4$ 453.1	50.36 50.03	1.11 0.95	3.09 2.84	360 (decomp.)
XI	$C_{19}H_9N_2O_4$ 325.2	70.13 70.14	2.90 2.89	4.31 4.08	256—258
XII	$C_{16}H_{11}NO_4$ 281.2	68.32 68.19	3.92 4.11	4.98 5.14	224—225
XIII	$C_{16}H_7Cl_4NO_4$ 419.0	45.86 46.12	1.69 1.91	3.34 3.09	234—235
XIV	$C_{16}H_{12}N_2O_7$ 346.3	55.44 55.58	3.46 3.71	8.08 8.13	201—204
XV	$C_{16}H_{13}NO_5$ 284.2	64.20 64.32	4.39 4.22	4.68 4.72	273—275
XVI	$C_{18}H_{16}O_6$ 328.2	65.85 65.52	4.92 4.82	– –	173—174
XVII	$C_{22}H_{15}NO_4S$ 389.3	67.84 67.62	3.89 3.54	3.60 3.39	279—280
XVIII	$C_{24}H_{15}NO_8S$ 477.3	60.32 60.08	3.14 3.24	2.93 2.63	310—312
XIX	$C_{17}H_{11}NO_5S_2$ 373.3	54.69 54.42	2.94 2.68	3.75 3.66	365—368
XX	$C_{14}H_{11}NO_4S_2$ 321.2	52.31 52.54	3.46 3.40	4.36 4.05	273—274
XXI	$C_{14}H_{13}NO_5S_2$ 339.2	49.54 49.74	3.87 4.09	4.13 3.84	297—298
XXII	$C_{18}H_{13}NO_4$ 307.2	70.31 70.50	4.23 4.21	4.55 4.54	250—253
XXIII	$C_{19}H_{15}NO_4$ 321.2	71.02 71.23	4.71 4.51	4.36 4.46	255—257
XXIV	$C_{18}H_{13}NO_5$ 323.2	66.86 66.52	4.06 4.19	4.33 4.28	269—271
XXV	$C_{18}H_{12}ClNO_4$ 341.7	63.25 63.38	3.55 3.35	4.10 4.22	270—272
XXVI	$C_{18}H_{12}BrNO_4$ 386.2	55.97 55.62	3.14 3.07	3.63 3.41	261—263
XXVII	$C_{20}H_{17}NO_4$ 335.3	71.62 71.41	5.12 5.22	4.18 4.01	256—259
XXVIII	$C_{22}H_{15}NO_4$ 357.3	73.96 74.25	4.17 4.17	3.92 3.92	300—302
XXIX	$C_{19}H_{17}NO_5$ 339.3	67.25 67.46	5.01 4.89	4.12 3.92	240—242
XXX	$C_{18}H_{15}NO_6$ 341.3	63.30 63.54	4.39 4.18	4.10 4.21	243—246
XXXI	$C_{21}H_{20}O_6$ 368.3	68.46 68.27	5.48 5.34	– –	159—161
XXXII	$C_{20}H_{18}O_7$ 370.3	64.85 64.62	4.91 4.86	– –	175—176
XXXIII	$C_{22}H_{22}O_6$ 382.4	69.09 68.82	5.81 5.84	– –	189—190
XXXIV	$C_{19}H_{15}NO_4$ 321.2	71.02 70.79	4.71 5.01	4.38 4.16	252—254

Table 1 (Continued)

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	M.p. °C
XXXV	$C_{20}H_{17}NO_4$	71.98	5.12	4.18	260—263
	335.2	71.68	4.92	4.06	
XXXVI	$C_{19}H_{14}ClNO_4$	64.13	3.97	3.94	170—172
	355.7	64.12	3.83	3.69	
XXXVII	$C_{23}H_{17}NO_4$	74.38	4.61	3.77	290—292
	371.3	74.14	4.69	3.74	
XXXVIII	$C_{20}H_{19}NO_5$	67.98	5.38	3.96	200—203
	353.3	67.94	5.16	3.79	
XXXIX	$C_{19}H_{17}NO_6$	64.16	4.78	3.56	219—221
	355.3	64.32	4.32	3.64	
XL	$C_{19}H_{14}BrNO_4$	57.01	3.53	3.50	238—240
	400.3	57.21	3.62	3.54	
XLI	$C_{20}H_{16}ClNO_4$	61.88	4.64	3.61	265—266
	387.8	61.85	4.48	3.45	
XLII	$C_{21}H_{10}BrNO_4$	60.02	2.40	3.33	298—301
	420.2	59.81	2.27	3.08	
XLIII	$C_{21}H_{11}NO_5$	70.58	3.11	3.98	242—243
	354.3	70.42	3.16	3.71	
XLIV	$C_{23}H_{15}NO_4$	74.78	4.10	3.79	255—257
	369.3	74.52	4.01	3.70	
XLV	$C_{22}H_{12}ClNO_4$	67.78	3.11	3.59	293—295
	389.6	67.71	2.97	3.50	
XLVI	$C_{22}H_{15}NO_5$	70.78	4.07	3.74	235—237
	373.4	70.62	3.94	3.56	
XLVII	$C_{21}H_{12}ClNO_5$	63.99	3.04	3.55	287—289
	393.8	63.77	2.96	3.45	

^{1}H NMR spectrum ($CHCl_3$, in DMSO*), δ: *XVI*: 1.32—1.50 (t, 3H), 1.79 (s, 6H), 4.29—4.55 (q, 2H), 7.83 (s, 1H), 7.88—7.97 (m, 4H); *XXI**: 1.40 (s, 6H), 3.03 (s, 3H), 3.76 (s, 3H), 6.87 (s, 1H), 7.75 (s, 4H); *XXXI*: 1.45 (t, 3H), 1.66 (s, 6H), 2.42 (s, 3H),4.35 (q, 2H), 7.32—7.44 (m, 3H), 7.99—8.24 (m, 3H); *XXXIII*: 1.43 (t, 3H), 1.66 (s, 6H), 2.33 (m, 6H), 4.31 (q, 2H), 7.21 (s, 1H, H-8), 7.32 (s, 1H, H-5), 7.94—8.22 (m, 3H, H-2, H-9,H-10).

The results of the tests concerning activity against Human Immunodeficiency Virus (HIV) indicated that the compounds were inactive.

EXPERIMENTAL

Melting points were determined on a Kofler hotplate apparatus and elemental analysis data are listed in Table 1.

IR spectra were taken in nujol, using a Specord IR-75 instrument. ^{1}H NMR spectra were measured in DMSO (saturated solutions) on Tesla BS 487 (80 MHz) spectrometer.

The herbicidal tests were carried out according to [5], the fungicidal tests according to [6], and the antifungal activity against human pathogenic dermatophytes and micromycetes was found according to [7]. The tests of the growth-regulating effects on *Cucumis sativus* were realized using the method described in [8], the effects of compounds on growth and chlorophyll production in algae *Chlorella vulgaris* were investigated according to [9]. The tests concerning anti-HIV activity of the compounds were carried out according to [10] in the National Cancer Institute in Bethesda (USA).

The following starting compounds (*II*), 2-R^5-3,4,4-trimethyl-2-buten-4-olide derivatives (R^5 = cyano, ethoxycarbonyl and benzothiazolyl) were prepared according to [11—13] ; 2-cyano-3,5,5-trimethyl-2-penten-5-olide according to [14], 3-cyano-4-methylcoumarin according to [12], and 3-formylchromones (*IV*) according to the Nohara method [15].

Derivatives of Phthalide

Method a (for derivatives *V—VII, IX—XIII, XVI—XVIII, XX*): The mixture of phthalic anhydride derivative *I* (10 mmol), lactone *II* (10 mmol), acetic anhydride (3 cm^3), and potassium acetate (1 mmol) was stirred and heated to 110—120 °C for 2 h to remove reaction water. After cooling to 25 °C, the product was diluted with cold aqueous solution of $NaHCO_3$ (2 mass %, 50 cm^3) and stirred for 1 h. Insoluble portion was separated, dried and crystallized from the mixture ethanol—dimethyl sulfoxide.

Method b (for derivatives *VIII, XIV—XVI, XIX, XXI*): The mixture of phthalic anhydride derivative *I* (10 mmol), lactone *II* (10 mmol), and potassium acetate (1 mmol) was stirred for 2 h at 150—160 °C. After

cooling the mixture was diluted with aqueous solution of $NaHCO_3$ (2 mass %, 70 cm^3), stirred for 1 h and filtered off. The product was crystallized from the mixture ethanol—dimethyl sulfoxide.

Derivatives of 4*H*-4-Oxochromene

Method a (for derivatives *XXII—XXVIII, XXXI—XXXVII, XLII— XLV*): The mixture of 3-formylchromone derivative *IV* (3 mmol), lactone *II* (3.2 mmol), acetic anhydride (5 cm^3), and potassium acetate (0.3 mmol) was stirred and heated at 80—90 °C for 3 h. After cooling the mixture was poured into cool water (50 cm^3) and stirred for 1 h. The precipitate was sucked off and recrystallized from ethanol, chloroform or dimethyl sulfoxide.

Method b (for derivatives *XXXI, XXXII, XXXVIII—XLI, XLVI, XLVII*): The mixture of 3-formylchromone derivative *IV* (3 mmol), lactone *II* (3.2 mmol), and potassium acetate (0.3 mmol) was dissolved in hot toluene and refluxed for 4 h. Toluene was distilled off and the solid was recrystallized from the mixture ethanol—dimethyl sulfoxide.

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