Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), www.mdpi.org/ecsoc-4.htm, September 1-30, 2000

[C0009]

Synthesis and antialgal effect of 2-substituted 5,6-dihydro-4,7-dithiaindane-1,3-diones

***Ruzena Cizmarikova*[1], *Katarina Kralova*[2], *Pavol Hrnciar*[3]**

[1]Department of Chemical Theory of Drugs, Faculty of Pharmacy, Comenius University, Kalinciakova 8, SK-832 32 Bratislava, Slovakia., Tel. 421 7 50259315
E-mail: Cizmarikova@fpharm.uniba.sk

[2]Institute of Chemistry and [3]Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, Mlynska dolina CH-2, SK-842 15 Bratislava, E-mail: kralova@fns.uniba.sk

Received: 6 August 2000 / Uploaded: 9 August

Abstracts

Derivatives of indane-1,3-diones are compounds showing interesting properties not only from theoretical view. Some 2-arylindane-1,3-diones are used as anticoagulants, dyes, polymerization modifiers and rodenticides. This study deals with synthesis, spectral and antialgal properties of new substituted 2-(5-aryl-2-thenylidene- or 2- furfurylidene)-5,6-dihydro-4,7-dithiaindane-1,3-diones **II.**

Keywords: cyclic 1,3-diketone, indane-1,3-dione , dithiaindane-1,3-dione, condensation reaction, antialgal effect, *Chlorella vulgaris*

Introduction

Indane-1,3-diones belong to the cyclic diketones. The presence of the adjacent carbonyl groups polarizes methylenegroup , which can gives a lot of reaction of the C-acids [1,2,3]. Among these reaction belongs reaction with the carbonyl compounds [4,5] - the Knoevenagel condensation.
2-(5-phenyl-2-furfurylidene - or -2-thenylidene)-5,6-dihydro-4,7-dithiaindane-1,3-diones were prepared by synthesis 5,6-dihydro-4,7-dithiandane-1,3-dione with substituted 5-phenylthiophene-2-carbaldehyde or 5-phenylfurane-2-carbaldehyde, utilizing piperidine as catalyst. The other aim of this study was to investigate the inhibition of chlorophyll production in the algal suspension of *Chlorela vulgaris* .

Results and discussion

The obtained compounds II (1t-9t., 1f-12f) with different colour intensity (from yellow to red) possessing high melting points (Tables 1,2) were crystallized from acetic acid or propan-2-one. The electronic spectra of **II** revealed three absorption bands with l_{max} = 210-215 nm, 260-280 nm, and 410-455 nm. For all the prepared compounds the position of the band at the longest wavelengths (410-455 nm) was mostly influenced by the nature of substituent X. The compounds bearing an electron-donating substituent on the phenyl ring in position 4 showed a significant bathochromic shift. This was not observed for the compounds with the same substituent in position 3. All compounds, independently on the position of substituent X on the phenyl ring, were intensively coloured (Tables 1,2).
The compounds **II** showed two bands (Tables.1,2) in the region of the stretching vibration of carbonyl group belonging to symmetrical and asymmetrical vibration of the C=O group of the b-dicarbonyl system.
In the ^{1}H NMR spectra the signal of the methylene group was at d = 3.34 ppm (in the group SCH_2CH_2S) and 7.30-7.54 ppm (for =CH group) (Table 3).
For tested compounds with Z = S the dependence of IC_{50} on the lipohilicity of substituent X was linear and the increase in the lipophilicity led to the decrease in the antialgal activity against *Chlorella vulgaris*. It can be assumed that this is connected with the restriction of the passage of more lipophilic compounds through the hydrophilic regions of algal thylakoid membranes and consecutive loss of their number reaching the site of inhibitory action. The compounds with Z = O substituted in position 2 (X = 2-Cl, 2-NO_2) exhibited rather lower inhibitory activity than the comparable compounds with Z = S substituted in position 4.
The previously prepared structurally similar benzylidene derivatives[4] did not affect chlorophyll production in *Chlorella vulgaris*. Thus, it can be concluded that for antialgal activity of the compounds the presence of heteroatom (S, O) in the molecule is favourable (Table 4).

Experimental

The starting material for both series was 5,6-dihydro-4,7-dithiaindane-1,3-dione **I** which was prepared by the Gabriel modification of the Perkin synthesis from 5,6-dihydro-1,4,-dithiine-2,3-dicarboxylic anhydride [6] (Scheme 1). Treatment of **I** with substituted 5-phenylthiophene-2-carbaldehyde or 5-phenylfurane-2-carbaldehyde in 96 % ethanol, utilizing piperidine as catalyst, afforded 2-(5-aryl-2-thenylidene)- or -2-furfurylidene)-5,6-dihydro-4,7-dithiaindane-1,3-diones **II**. Under these conditions the aromatic aldehydes reacted with **I** in the ratio 1: 1 (Scheme 2). The nitro derivatives, thus obtained, were reduced with $SnCl_2$ in acetic acid to the corresponding amino derivatives. The Zeissel demethylation of the methoxy derivatives using HBr acid gave the corresponding phenols[4].
Melting points were determined by a Kofler hot bench and are uncorrected.
Electronic spectra were measured on a spectrometer Hewlett-Paccard 8452A in methanol in the concentration 10^{-5} mol.dm^{-3}. Infrared spectra of prepared compounds were measured in the region 1800-1600 cm^{-1} on a spectrophotometer FTIR IMPACT 400 D (Nicolet) as 10^{-2} mol.dm^{-3} con-centration in tetrachloromethane .
^{1}H-NMR spectra of prepared compounds dissolved in deuterochloroform were measured on spectrometer Tesla BS-487 A with frequency 80 MHz using internal standard TMS.

Synthesis of 2-substituted 4,7-dithia-5,6-dihydroindane-1,3-diones II

Z= O, S X= 4-OCH_3 , 4-CH_3 , 3-CH_3, H, 2-Cl, 4-Cl, 4-Br, 3-F, 3-Br, 2-NO_2, 3-NO_2, 4-NO_2

Into a flask provided with a reflux condenser dithiaindandione (3.72 g, 0.02 mol), the appropriate aldehyde (0.02 mole), and 98% ethanol (50-80ml) were added. After dissolving the components, piperidine (2 drops) was added and reaction and reaction mixture with substituted 5-phe-nylthiophene-2-carbaldehyde was refluxed for 10 min. Reaction with substituted 5 phenylfuryl-2-carbaldehyde was carried at 20^0C for 10 minutes. Acetic acid (2 drops) was added into the cooled solution and the precipitated crude product was crystallized from propan-2-one or acetic acid.
Yield 70-90 %.

X= OH

The metoxyderivatives (0.01 mol), acetic acid (15 ml), and 38% hydrobromic acid (40 ml) were heated for 3 hrs under reflux. After cooling, hot water (250 ml) was added and crude product was crystallized from acetic acid. Yield 65%.

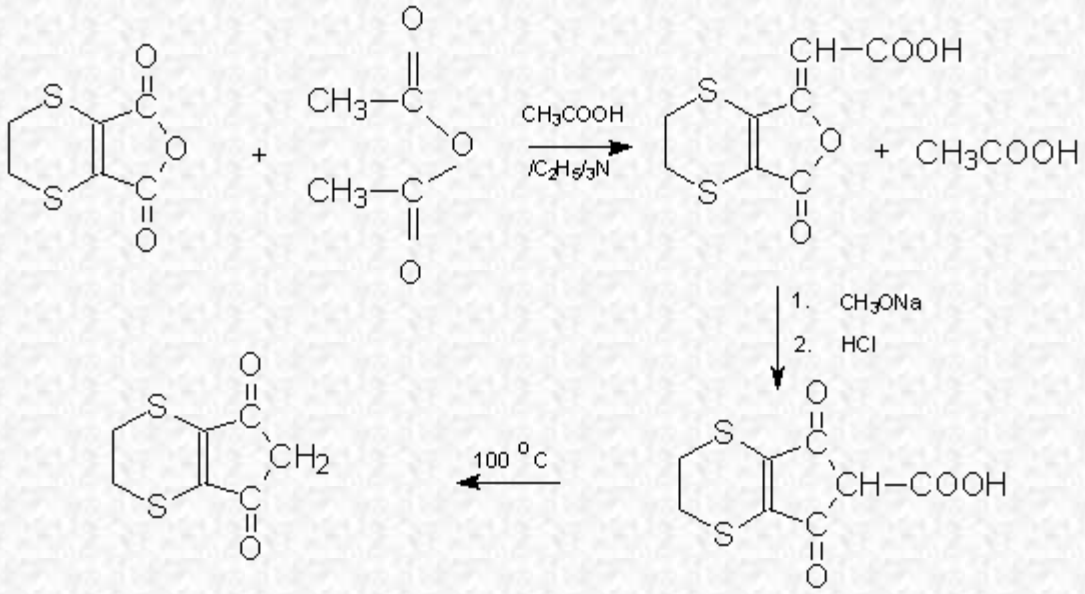
X= NH_2

Into a three-necked flask fitted with a stirrer and condenser, tin chloride dihydrate (1.5 g), acetic acid (10 ml), and hydrochloric acid (2 ml) were added. When tin dichloride was dissolved, nitroderivatives (0.002 mol) was added and reaction mixture was stirred at 80^0 C for 2 hrs. After cooling, the salts of the corresponding amine precipitated and was transferred into free amine by washing with ammonia. The crude product was crystallized from propan-2-one. Yield 75%.

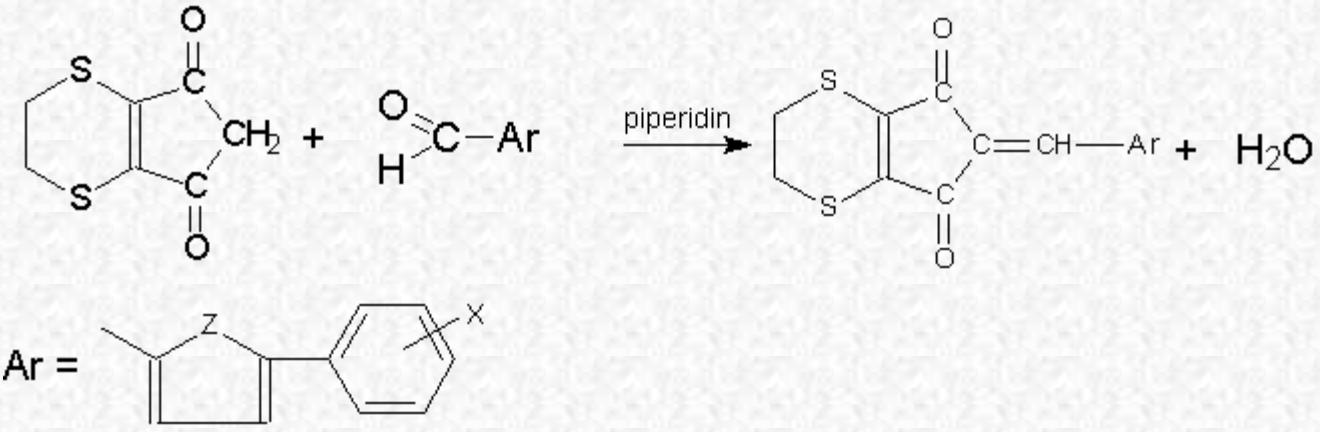
Antialgal effect

The effect of these compounds from the prepared series on algal chlorophyll (Chl) production has been investigated in statically cultivated *Chlorella vulgaris* (photoperiod 16 h light/ 8h dark; illumination: 5 000 lx; pH = 7.2; Chl content at beginning of cultivation: 0.5 mg dm^{-3}) at room temperature according to [7]. Chl content of algal suspensions was extracted into *N*,*N*-dimethylformamide and determined spectrophotometrically after 7 days of cultivation [8]. Because of low water solubility of the tested compounds these were dissolved in dimethyl sulfoxide (DMSO). The photosynthesis-inhibiting activity of **II** was expressed by IC_{50} values, *i.e*. by molar concentrations of inhibitors causing 50 % decrease of biological activity with respect to the untreated control (Table 1).

Scheme 1 Synthesis of 5,6-dihydro-4,7-dithiaindane-1,3-dione I



Scheme 2 Synthesis of 2- substituted 5,6-dihydro- 4,7-dithiaindane-1,3-diones II - The Knoevenagel condensation



1t-9t., 1f-14f
Z = O, S X= 4-OH, 4-OCH_3, 4-CH_3, 3-CH_3, 3-NH_2, H, 2-Cl, 4-Cl, 4-Br, 3-F, 3-Br, 2-NO_2, 3-NO_2, 4-NO_2,

Table 1. Characterization of prepared 2-(5-phenyl- 2-thenylidene) -5,6- dihydro-4,7-dithiaindane-1,3-diones II

No.	X	Formula M_r	M.p. ^oC Solvent	l_{max}	log e	$n_{s(C=O)}$	$n_{as(C=O)}$
1t	4-NH_2	$C_{18}H_{13}N\,O_3S_3$ 371.50	236-7 a	450	4.54	1723	1677
2t	4-OCH_3	$C_{19}H_{14}O_3S_3$ 386.51	230-2 b	445	4.54	1723	1679
3t	4-CH_3	$C_{19}H_{14}O_2S_3$ 370,51	248-9 b	436	4.36	1725	1678
4t	3-CH_3	$C_{19}H_{14}O_2S_3$ 370.51	180-2 b	430	4.39	1725	1679
5t	-H	$C_{18}H_{12}O_2S_3$ 356,49	201-3 b	430	4.43	1725	1679
6t	4-Cl	$C_{18}H_{11}O_2S_3\,Cl$ 390,93	244-6 b	425	4.06	1725	1680
7t	4-Br	$C_{18}H_{11}O_2S_3\,Br$ 435,39	254-6 b	442	4.03	1726	1680
8t	3-Br	$C_{18}H_{11}O_2S_3\,Br$ 435,39	203-5 b	432	4.07	1726	1680
9t	4-NO_2	$C_{18}H_{11}O_4NS_3$ 401,48	280-2 b	413	4.08	1726	1682

a-propan-2-one ., b- acetic acid e in $l.mol^{-1}.cm^{-1}$ n in cm^{-1} l_{max} in nm

Table 2. Characterization of the prepared 2-(5-phenyl-2-furfurylidene)-

- 5,6- dihydro-4,7-dithiaindane-1,3-dione II

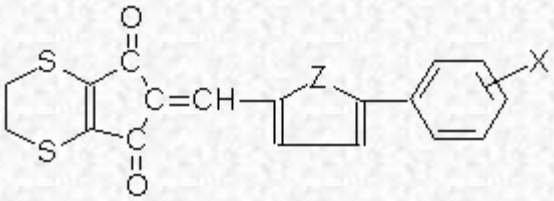
No.	X	Formula M_r	M.p.^{0}C Solvent	l_{max}	log e	$n_{s(C=O)}$	$n_{as(C=O)}$
1f	4-OH	$C_{18}H_{12}O_4S_2$ 340.42	268-9 a	455	4.57	1721	1675
2f	4-OCH_3	$C_{19}H_{14}O_4S_2$ 356.42	203-5 b	450	4.65	1722	1676
3f	4-CH_3	$C_{19}H_{14}O_4S_2$ 354.45	263-5 b	433	4.66	1724	1677
4f	3-NH_2	$C_{18}H_{13}O_3NS_2$ 355.44	218-9 b	432	4.63	1724	1676
5f	-H	$C_{18}H_{12}O_3S_2$ 340.42	243-5 b	430	4.62	1724	1677
6f	4-Cl	$C_{18}H_{11}O_3S_2Cl$ 374.87	274-5 b	432	4.06	1724	1677
7f	4-Br	$C_{18}H_{11}O_3S_2Br$ 479.32	267-9 b	435	4.11	1724	1678
8f	3-F	$C_{18}H_{11}O_3S_2F$ 418.42	245-7 b	432	4.47	1715[c]	1678[c]
9f	3-Cl	$C_{18}H_{11}O_3S_2Cl$ 374.87	244-6 b	427	4.48	1725	1678
10f	3-Br	$C_{18}H_{11}O_3S_2Br$ 479.32	254-5 b	430	4.38	1725	1679
11f	3-NO_2	$C_{18}H_{11}NO_5S_2$ 385.42	310-2 a	425	4.36	1718[c]	1673[c]
12f	4-NO_2	$C_{18}H_{11}NO_5S_2$ 385.42	314-6 a	442	4.58	1719[c]	1674[c]
13f	2-NO_2	$C_{18}H_{11}NO_5S_2$ 385.42	228-230 a	426	5.46	1719	1675[c]
14f	2-Cl	$C_{18}H_{11}O_3S_2Cl$ 374.87	214-5 a	428	4.29	1720	1670

a - propan-2-one., b- acetic acid c-for the low solubility spectrum was measured in chloroform
The results of elementary analyses (C,H,S,X) are in agreement with the calculated values.

Table 3. ^{1}H-NMR spectra

Z	X	d (ppm) $S(CH_2)_2S$	=CH	$CH_{arom.}$	X (H)
S	-H	3.34 4H	7.35 1H	7.40-7.88 7H	
S	4-Br	3.34 4H	7.54 1H	7.38-7.85 6H	
S	4-OCH_3	3.34 4H	7.30 1H	7.54-7.85 6H	3.38 3H
S	4-CH_3	3.34 4H	7.32 1H	7.54-7.86 6H	2.38 3H
S	4-NO_2	3.34 4H	7.49 1H	7.60-8.40 6H	
O	2-Cl	3.37 4H	7.37 1H	7.33-8.23 6H	
O	2-NO_2	3.31 4H	7.31 1H	7.33-8.26 6H	

Table 4. Inhibition of chlorophyll in Chlorella vulgaris



Z	X	IC_{50} [mmol . dm^{-3}]	Z	X	IC_{50} [mmol . dm^{-3}]
S	-H	46.6	O	2-Cl	97.9
S	4-Cl	71.4	O	2-NO_2	88.6
S	4-Br	74.9	O	4-Br	84.2
S	4-CH_3	53.3	O	4-OH	131.4
S	4-OCH_3	42.1	O	4-CH_3	53.5
S	4-NO_2	52.3			

Acknowledgements. Our thank are due to prof. Fisera and prof. Krutosikova for the supply of substituted 5-phenyl-2-thiophenecarbaldehyde and 5-.phenyl-2-furancarbaldehyde used in the preparation of the compounds under study.

This study was supported by Scientific Grant Agency of Ministry of Education, Slovak Republic (grants No. 1/ 7277/20 and 1/7262/20)

References

1. Artico, M.; Di Santo, R.; Costi, R..; et al.; *J.Med. Chem*. **1998**,41, 3948.
2. Sarhan, A,A.; Afsah, E,M.; Abdelaal, M,Y.; Ibrahim, M,R.; *React. Funct. Polym*. **1997**, 32, 231.
3. Cizmarikova ,R.; Hrnciar, P.; Cupkova, V.; **1990** *CS* 276 674
4. Hrnciar P.; Cizmarikova R.; *Chem. Zvesti* **1975**, 29, 836-842.
5. Perjessy, A., Hrnciar, P., Frimm, R., Fisera, L.: *Tetrahedron* **1972**, 28, 3781
6. Hrnciar P.; Sokolova R.; *Monatsh Chem*. **1973**, 104, 1224-1230.
7. Kralova K.; Sersen F.; Melnik M.; *J. Trace Microprobe Techn*. **1998**, 16, 491.
8. .Inskeep W. P., Bloom P. R., *Plant Physiol*. **1985**, 77, 483.
