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SYNTHESIS OF 6-SUBSTITUTED-2-(4-METHOXYPHENYL)-2,3-DIHYDROPHENALEN-1,3-DIONES AND THEIR DERIVATIVES

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ABSTRACT

A condensation of 1,8-naphtalic anhydride (Ia), 4-bromo- (Ib), 4-acetyl- (Ic), 4-nitro- (Id), 4-piperidino- (Ie), 4-morpholino- (If), 4-pyrrolidino- (Ig) naphtalic anhydride with 4-methoxyphenylacetic acid is performed. The fusion of the anhydrides Ia-Ig with 4-methoxyphenylacetic acid in the presence of anhydrous CH_3COONa, leads to formation of the corresponding 6-substituted-2-(4-methoxyphenyl)-2,3-dihydrophenalen-1,3-diones and 7-substituted-1,3-dihydronaphto-(1,8-c,d)-pyran-1-ones simultaneously. The structures of the newly synthesized compounds are confirmed by elemental analysis, IR-, UV- and NMR-spectral data.

Keywords: 2,3-dihydrophenalen-1,3-diones, 4-methoxyphenylacetic acid

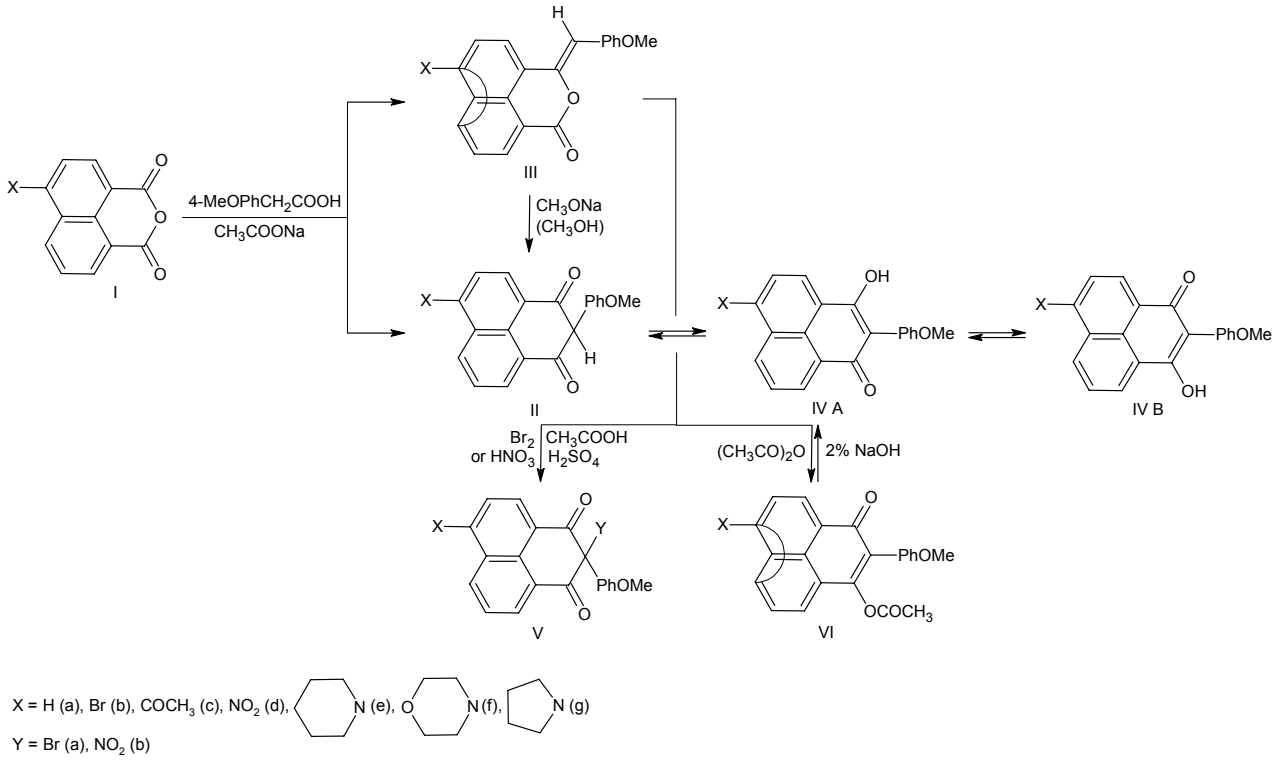
INTRODUCTION

Derivatives of 2,3-dihydrophenalen-1,3-diones have biological activity. They are used as dyes and analytical reagents as well as reagents in the fine organic synthesis [1-3]. These characteristics bring our attention to studies on condensation of 4-substituted naphthalic anhydride with 4-methoxyphenylacetic acid, finding optimal conditions for the course of the reaction, obtaining new 2,3-dihydrophenalen-1,3-dion derivatives, and through them synthesising new products with certain physiological activity.

A synthesis of various 6-substituted 2-phenyl-2,3-dihydrophenalen-1,3-diones through condensation of naphtalic anhydrides with phenylacetic acid was earlier reported [4-6].

A condensation of 1,8-naphtalic anhydride (Ia), 4-bromo- (Ib), 4-acetyl- (Ic), 4-nitro- (Id), 4-piperidino- (Ie), 4-morpholino- (If), 4-pyrrolidino- (Ig) naphtalic anhydride with 4-methoxyphenylacetic acid (Scheme 1) is accomplished in this

paper. The structures of the newly synthesized compounds are confirmed by elemental analysis (Table 2), IR- (Table 3), UV- (Table 4) and NMR- spectral data.



Scheme 1

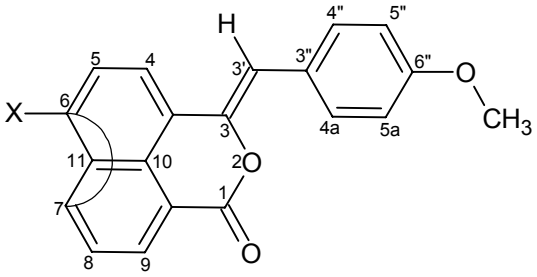


Figure 1. *Compounds III*

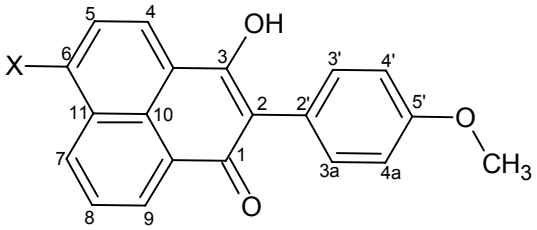


Figure 2. *Compounds IVA*

RESULTS AND DISCUSSION

The fusion of anhydrides Ia-Ig with 4-methoxyphenylacetic acid in the presence of anhydrous sodium acetate leads to formation of the respective 6-substituted-2-(4-methoxiphenyl)-2,3-dihydrophenalen-1,3-diones (Table 1). Alongside with these products are formed 7-substituted-1,3-dihydronaphto-(1,8-c,d)-pyran-1-ones (IIIa-IIIg), which as a result of thermal rearrangement under the reaction with sodium methylate or under reaction with aqueous solution of ammonium carbonate, easily isomerised to II [7]. Compounds III have luminophore properties, the place of their substitutes has already been proved by us in a former study [8] by the Overhauser method.

The relatively low yield of 6-acetyl derivative IIc is obviously caused by the fact that under these condensation conditions a partial decomposition of the initial Ic anhydride takes place. During the conducted tests for determination of optimal conditions for obtaining of IIa-IIg we found out that under 180°C condensation runs slowly and the yield of end products is low, while at temperatures higher than 230°C a intense resination has been observed. The presence of by-products has been identified via thin layer chromatography when the optimal reaction temperature is within the interval 180-230°C, and the duration of the heating is 2-3 hours. For the naphtalic anhydrides Ib,c,d containing in their molecule electron acceptor substitutes this temperature is 180-200°C, while for anhydrides Ie,f,g containing electron donor substitutes the optimal temperature for their condensation with 4-methoxiphenylacetic acid is 210-230°C.

Heating duration for more than 3 hours leads to formation of by-products with unidentified structures, and the yields drop down significantly. Heating duration of less than 2 hours leads to increase in yields of the respective pyranones IIIa-IIIg.

Table 1. *Condensation of 4-substituted naphtalic anhydride with 4-methoxyphenylacetic acid*

Com-poud I	Reaction conditions			Reaction products					
				II-IV			III		
	Cata-lyser	Temp. (°C)	Duration (h)	M.p. (°C)	Rf*	Yield (%)	M.p. (°C)	Rf*	Yield (%)
a	CH_3COONa	240	2	224-5	0.43	25	168-9	0.60	29
b		190	2	227-8	0.68	31	139-40	0.90	27
c		190	2	231-2	0.63	33	162-3	0.85	21
d		190	2	265-6	0.70	20	187-8	0.87	16
e		220	3	183-4	0.66	23	148-9	0.91	32
f		230	3	221-2	0.69	25	170-1	0.85	25
g		230	3	166-7	0.81	19	192-3	0.62	29

** benzene : ethanol = 5 : 1*

The colour of compound IIb is light red, IIc,d - light brown, and IIa,e,f,g are orange-red products.

Table 2. *Elemental analysis data of the compounds III-VI*

Compound	C (%)		H (%)		N (%)		Br (%)	
	calcd.	found	calcd.	found	calcd.	found	calcd.	found
IIIa	79.46	79.31	4.67	4.48				
IIIb	63.01	62.89	3.44	3.31			20.96	20.67
IIIc	76.73	76.58	4.68	4.53				
IIId	69.16	69.02	3.77	3.63	4.03	3.78		
IIIe	77.90	77.77	6.01	5.89	3.63	3.47		
IIIf	74.40	74.16	5.46	5.41	3.61	3.55		
IIIg	77.60	77.48	5.70	5.47	3.77	3.67		
IVa	79.46	79.26	4.67	4.53				
IVb	63.01	62.88	3.44	3.27			20.96	20.81
IVc	76.73	76.54	4.68	4.59				
IVd	69.16	69.11	3.77	3.69	4.03	3.83		
IVe	77.90	77.80	6.01	5.83	3.63	3.45		
IVf	74.40	74.27	5.46	5.35	3.61	3.48		
IVg	77.60	77.53	5.70	5.61	3.77	3.63		
Va,a	63.10	62.74	3.44	3.38			20.96	20.67
Va,b	69.16	68.88	3.77	3.54	4.03	3.96		
Vb,a	52.2	51.94	2.63	2.48			34.73	34.5
Vb,b	56.36	56.28	2.84	2.75	3.29	3.19	18.75	18.56
VIa	76.51	76.43	4.96	4.86				

The compounds II have dual reaction ability: during nitration and bromination they form 2-substituted products Va-Vg, while during acylation - 3-substituted products VIa-VIg. The last reaction reveals the possibility for the existence of the products from condensation in enol form IV.

The comparison of the spectral data of compounds II with these of compounds V and VI, sugests that compounds II exist in a close to enol form. IR-spectra of the compounds IIa-IIg are characterized for absorption of carbonyl group in the interval 1624-1632 cm^{-1}, which is typical for the enol compounds VI. This is why, the spectra taken in chloroform solution allow the observation of absorption at 3493-3499 cm^{-1}, determined by the presence of enol hydroxyl group in the form IV.

In UV-spectra of compounds IIa-IIg a long-wave maximum of absorption appears, evidencing in favour of the enol form IV. UV-spectra of the anion form IIa-IIg [ethanol (95%): aqueous ammonia (25%) 10:1] are similar to the specta of the enol form, but with batochrome shift, which is in conformity with the published data [9]. We can conclude on the aforesaid that products of condensation of naphthalic anhydrides with 4-methoxyphenylacetic acid, exist in the enol form IV. However, the position of the substitute in the naphthalic nucleus remains unidentified, i.e. the direction of the enolisation leads to formation of 6- (IVA) and/or 7-substituted phenalenon (IVB). This fact was found out by us in the reaction of phenalenones with $(CH_3CO)_2O$, through which acetoxiphenalenones (VI) are formed, which was proved

chromatographically, which, when treated with 2% NaOH, turn into product (IV).

Table 3. *Characteristic frequencies of compounds III-VI (ν_{cm}^{-1})*

№	ν_{OH}	ν_{CH} (arom.)	ν_{CH} (alif.)	$\nu_{OC=O}$	$\nu_{C=O}$	$\nu_{C=C}$
IIIa		3055	2926		1740	
IIIb		3051	2932		1741	
IIIc		3053	2933		1738, 1698	
IIId		3059	2929		1736	
IIIe		3051	2931		1728	
IIIf		3063	2956		1725	
IIIg		3059	2948		1728	
IVa	3495	3053	2953		1628	1605
IVb	3493	3051	2951		1625	1603
IVc	3498	3049	2932		1621	1608
IVd	3495	3056	2933		1662	1604
IVe	3496	3050	2933		1626	1602
IVf	3497	3054	2925		1618	1599
IVg	3494	3054	2926		1621	1601
Va,a		3054	2932		1702, 1685	
Va,b		3051	2927		1710, 1684	
Vb,a		3053	2930		1704, 1685	
Vb,b		3058	2938		1712, 1686	
VIa		3056	2936	1773	1639	1606

Table 4. *UV-spectral data of compounds III and IV*

Compound	λ_{max} (nm)		
	chloroform	**ethanol**	**ethanol : aqueous ammonia**
IIIa		269, 279, 317, 404	
IIIb		279, 343, 453	
IIIc		334	
IIId		276, 337, 454	
IIIe		272, 340, 414	
IIIf		269, 326, 409	
IIIg		280, 333, 433	
IVa	259, 347, 411	264, 346, 418	290, 343, 360, 462
IVb	257, 362, 414	281, 350, 422	292, 348, 366
IVc	277, 351, 419	281, 346	284, 342
IVd	359	276, 357, 448	356
IVe	260, 348, 447	257, 345, 402	285, 345, 396
IVf	271, 342, 401	264, 341, 400	330
IVg	259, 345, 444	255, 340, 399	281, 342, 395

EXPERIMENTAL

All chemicals used are purchased from Merck and Fluka.

The melting points are determined with a Koffler apparatus.

The elemental analysis data are obtained with an automatic analyzer Carlo Erba 1106.

The purity of the compounds is checked by thin layer chromatography on Kieselgel 60 F_{254}, 0.2 mm Merck plates, eluent system (vol. ratio): benzene: ethanol = 5: 1.

IR spectra are taken on spectrometers Perkin-Elmer FTIR-1750 in KBr discs and Bruker-113 in chloroform solution.

NMR spectra are taken on a Bruker DRX-250 spectrometer.

UV-Vis spectra are taken on a spectrometer Camspec M 508.

Initial 4-substituted naphtalic anhydrides are synthesized on the basis of publications [10,11].

I. General synthesis of 6-substituted-2-(4-methoxiphenyl)-2,3-dihydrophenalen-1,3-diones and 3-(4-methoxiphenylmethylene)-1H,3H-naphto-(1,8-c,d)-pyran-1-ones

a) 0.04 moles of 4-substituted naphtalic anhydride, 0.12 moles 4-methoxyphenylacetic acid and 0.06 moles anhydrous sodium acetate are heated for 2-3 hours at temperatures of 190-240°C (Table 1). After cooling of the mixture, 500 ml 3% aqueous NH_3 are added. Then it is filtered and the filtrate is acidated with CH_3COOH to reach pH 6.5. As a result 6-substituted-2-(4-methoxiphenyl)-2,3-dihydrophenalen-1,3-diones are obtained. The precipitate is removed by filtration and recrystallized using an appropriate solvent.

After acidification of the filtrate to pH 1, a certain amount of non-reacted initial 4-substituted naphthalic anhydride has been isolated.

- *IVa:*

^{1}H-NMR (δ, $CDCl_3$, ppm): 3.43 (s, 3H, CH_3), 6.26 (s, 1H, OH), 7.2-7.7 (m, 4H, Ph), 7.83 (s, 2H, H-5, H-8), 8.29 (s, 2H, H-6, H-7), 8.41 (s, 2H, H-4, H-9)

^{13}C-NMR (δ, $CDCl_3$, ppm):, 38.6 (CH_3), 113.5 (C-2), 126.7 (C-5, C-8), 128.1 (C-4, C-9), 129.3 (C-4', C-4a), 130.6 (C-3', C-3a), 133.1 (C-6, C-7), 151.4 (C-3), 171.5 (C-1)

^{13}C-DEPT (δ, MeOH, ppm): 38.6 (CH_3), 126.7(C-5, C-8), 128.1 (C-4, C-9), 133.1 (C-6, C-7)

- *IVb:*

^{1}H-NMR (δ, $CDCl_3$, ppm): 3.49 (s, 3H, CH_3), 6.32 (s, 1H, OH), 7.15-7.68 (m, 4H, Ph), 7.72 (s, 1H, H-5), 7.91 (s, 1H, H-8), 8.15 (s, 1H, H-6), 8.26 (s, 1H, H-4), 8.30 (s, 1H, H-9)

^{13}C-NMR (δ, $CDCl_3$, ppm): 43.0 (CH_3), 112.0 (C-2), 123.7 (C-7), 128.7 (C-4), 129.0 (C-4', C-4a), 129.3 (C-3', C-3a), 130.3 (C-8), 131.0 (C-6), 133.1 (C-5), 154.3 (C-3), 173.5 (C-1)

^{13}C-DEPT (δ, MeOH, ppm): 43.0 (CH_3), 123.7 (C-7), 128.7 (C-4), 129.0 (C-4', C-4a), 129.3 (C-3', C-3a), 130.3 (C-8), 133.1 (C-5)

- *IVc:*

^{1}H-NMR (δ, $CDCl_3$, ppm): 3.12 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 6.11 (s, 1H, OH), 7.37-7.52 (m, 4H, Ph), 7.80 (s, 1H, H-8), 8.07 (s, 1H, H-5), 8.29 (s, 1H, H-4), 8.64 (s, 1H, H-9), 9.0 (s, 1H, H-7)

^{13}C-NMR (δ, $CDCl_3$, ppm): 44.0 (CH_3), 111.2 (C-2), 122.9 (C-7), 126.6 (C-4', C-4a), 127.7 (C-4), 128.7 (C-3', C-3a), 130.2 (C-8), 131.1 (C-6), 132.6 (C-5), 152.6 (C-3), 168.5 (C-1)

^{13}C-DEPT (δ, MeOH, ppm): 44.0 (CH_3), 122.9 (C-7), 126.6 (C-4', C-4a), 127.7 (C-4), 128.7 (C-3', C-3a), 130.2 (C-8), 132.6 (C-5)

- *IVd:*

^{1}H-NMR (δ, $CDCl_3$, ppm): 3.49 (s, 3H, CH_3), 6.84 (s, 1H, OH), 7.01-7.34 (m, 4H, Ph), 7.38 (s, 1H, H-5), 7.74 (s, 1H, H-8), 8.52 (s, 1H, H-4), 8.56 (s, 1H, H-7), 8.68 (s, 1H, H-9)

^{13}C-NMR (δ, $CDCl_3$, ppm): 38.0 (CH_3), 113.7 (C-2), 124.4 (C-7), 127.5 (C-4', C-4a), 128.0 (C-3', C-3a), 129.4 (C-4), 130.2 (C-8), 132.5 (C-6), 134.6 (C-5), 158.3 (C-3), 173.6 (C-1)

^{13}C-DEPT (δ, MeOH, ppm): 38.0 (CH_3), 124.4 (C-7), 127.5 (C-4', C-4a), 128.0 (C-3', C-3a), 129.4 (C-4), 130.2 (C-8), 134.6 (C-5)

- *IVe:*

^{1}H-NMR (δ, $CDCl_3$, ppm): 1.71-1.91 (m, 10H, H_x), 3.2 (s, 3H, CH_3), 7.06 (s, 1H, H-5), 7.25-7.46 (m, 4H, Ph), 7.7 (s, 1H, H-8), 8.11 (s, 1H, H-4), 8.47 (s, 1H, H-7), 8.64 (s, 1H, H-9)

^{13}C-NMR (δ, $CDCl_3$, ppm): 24.0-26.5 (CH_2, piperid. nucleus) 33.0 (CH_3), 115.0 (C-2), 123.4 (C-7), 125.5 (C-4', C-4a), 126.3 (C-3', C-3a), 126.8 (C-4), 127.8 (C-8), 128.2 (C-6), 132.1 (C-5), 159,6 (C-3), 169.9 (C-1)

^{13}C-DEPT (δ, MeOH, ppm): 24.0-26.5 (CH_2, piperid. nucleus) 33.0 (CH_3), 123.4 (C-7), 125.5 (C-4', C-4a), 126.3 (C-3', C-3a), 126.8 (C-4), 127.8 (C-8), 132.1 (C-5)

- *IVf:*

^{1}H-NMR (δ, $CDCl_3$, ppm): 1.69-1.88 (m, 8H, H_x), 3.29 (s, 3H, CH_3), 6.23 (s, H, OH), 7.18 (s, 1H, H-5), 7.25-7.48 (m, 4H, Ph), 7.73 (s, 1H, H-8), 8.15 (s, 1H, H-4), 8.50 (s, 1H, H-7), 8.63 (s, 1H, H-9)

^{13}C-NMR (δ, $CDCl_3$, ppm): 25.4-27.2 (CH_2, morph. nucleus), 41.0 (CH_3), 114.3 (C-2), 124.6 (C-7), 125.8 (C-4', C-4a), 126.2 (C-3', C-3a), 127.5 (C-4), 128.8 (C-8), 129.5 (C-6), 133.5 (C-5), 158.3 (C-3), 167.7 (C-1)

^{13}C-DEPT (δ, MeOH, ppm): 25.4-27.2 (CH_2, morph. nucleus), 41.0 (CH_3), 124.6 (C-7), 125.8 (C-4', C-4a), 126.2 (C-3', C-3a), 127.5 (C-4), 128.8 (C-8), 133.5 (C-5)

- *IVg:*

^{1}H-NMR (δ, $CDCl_3$, ppm): 1.68-1.92 (m, 8H, H_x), 3.33 (s, 3H, CH_3), 6.28 (s, 1H, OH), 7.16 (s, 1H, H-5), 7.18-7.53 (m, 4H, Ph), 7.74 (s, 1H, H-8), 8.09 (s, 1H, H-4), 8.43 (s, 1H, H-7), 8.58 (s, 1H, H-9)

^{13}C-NMR (δ, $CDCl_3$, ppm): 23.2-27.6 (CH_2, pyroll. nucleus), 38.0 (CH_3), 115.3 (C-2), 125.5 (C-4',C-4a), 126.6 (C-7), 127.8 (C-3', C-3a), 128.1 (C-4), 129.9 (C-8), 131.2 (C-6), 134.6 (C-5), 153.5 (C-3), 170.2 (C-1)

^{13}C-DEPT (δ, MeOH, ppm): 23.2-27.6 (CH_2, pyroll. nucleus), 38.0 (CH_3), 125.5 (C-4',C-4a), 126.6 (C-7), 127.8 (C-3', C-3a), 128.1 (C-4), 129.9 (C-8), 134.6 (C-5)

b) Following treatment with 3% aqueous NH_3, the residue is extracted on a Soxlete apparatus with petroleum ether, and as a result 3-(4-methoxiphenylmethylene)-1H,3H-naphto-(1,8-c,d)-pyran-1-ones are obtained (Table 1). These are recrystallized from ethanol.

- *IIIb:*

^{1}H-NMR (δ, $CDCl_3$, ppm): 3.20 (s, 3H, CH_3), 7.34-7.69 (m, 4H, Ph), 7.80-8.43 (m, 5H, napht. nucleus)

^{13}C-NMR (δ, $CDCl_3$, ppm): 123.7 (C-7), 124.5 (C-4", C-4a), 125.9 (C-5", C-5a), 127.5 (C-9), 128.7 (C-4), 130.3 (C-8), 130.5 (C-3'), 131.0 (C-6), 133.1 (C-5), 154.3 (C-3), 173.5 (C-1)

II. General synthesis of 6-substituted-2-(4-methoxiphenyl)-2,3-dihydrophenalen-1,3-diones

0.01 mol of 4-substituted naphtalic anhydride, 0.03 moles 4-methoxyphenylacetic acid and 0.015 moles anhydrous sodium acetate are heated for 2-3 hours, at temperatures of 190-240°C (Table 1). The mixture is cooled down to 50°C and 100 ml 3% sodium methylate in methanol is added. The mixture is refluxed for 30 minutes. The mixture is cooled down and 100 ml 5% aqueous solution of sodium acetate is added. The mixture is filtrated. The filtrate is neutralized with CH_3COOH and the precipitates obtained are filtered. Yields of end products vary from 52% for acetyl to 85% for piperidine derivatives. Their colours vary from light brown to red.

III. Synthesis of 6-substituted-2-nitro-2-(4-methoxiphenyl)-2,3-dihydrophenalen-1,3-diones (Va-g; Y=b)

0.0025 moles of the product IIa-g are dissolved in 18 ml CH_3COOH at 60°C. 0.005 moles of HNO_3 (d_{20}=1.36) in 2 ml CH_3COOH are added drop wise to the

reaction mixture. After cooling a light yellow product (Va-g; Y=b) is obtained in the reaction mixture which is recrystallized in CH_3COOH.

IV. Synthesis of 6-substituted-2-bromo-2-(4-methoxiphenyl)-2,3-dihydrophenalen-1,3-diones (Va-g; Y=a)

0.005 moles of IIa-IIg are dissolved in 20 ml CH_3COOH during heating. To the resulting reaction mixture, a solution of 0.005 moles bromine in 10 ml CH_3COOH is added drop wise at 50°C for 30 minutes. After 3 hours the reaction mixture is diluted with water and the precipitate is filtered. Thus obtained products (Va-g; Y=a) are light yellow coloured and they are recrystallized in ethanol.

V. Synthesis of 6- (or 7-) substituted-2-(4-methoxiphenyl)-3-acetoxiphenalenones (VI)

0.005 moles of II and 10 ml acetic anhydride are refluxed for 2 hours. The reaction mixture is poured down in 100 ml water, to obtain a product with yield (85-95%).

VI. Hydrolysis of the obtained acetoxiphenalenones

1 g of the product VI a-g is dissolved in 50 ml ethanol. 50 ml 2% NaOH is added and the mixture is refluxed for 2 hours. After distillation of the major part of the ethanol, the mixture is diluted with water and neutralized with CH_3COOH. The precipitate is filtered and recrystallized from an appropriate solvent. The product reveals the same physicochemical parameters as the products obtained through methods Ia and II.

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