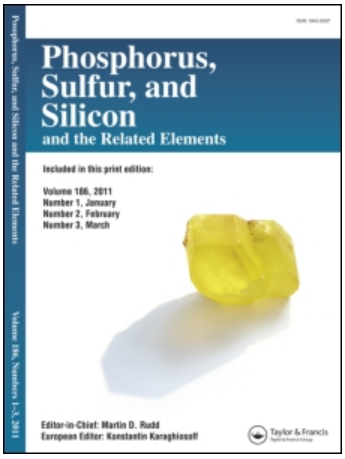

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STUDIES ON α-[6-(2'-METHOXYNAPHTHALENYL)-4-PHENYLPYRIMIDINYLTHIO]-β/-(4-PHENYLBENZOYL)PROPIONIC ACID AND THE BIOLOGICAL ACTIVITY OF SOME PRODUCTS

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STUDIES ON α-[6-(2′-METHOXYNAPHTHALENYL)-4-PHENYLPYRIMIDINYLTHIO]-β-(4-PHENYLBENZOYL)PROPIONIC ACID AND THE BIOLOGICAL ACTIVITY OF SOME PRODUCTS

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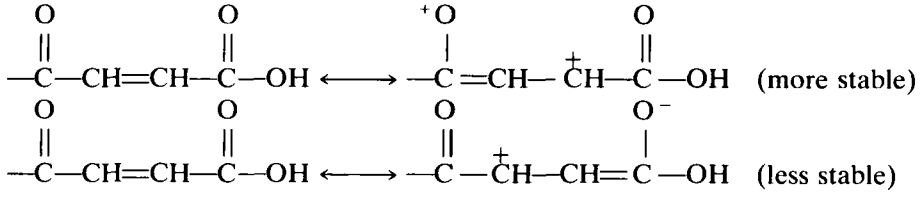
β-(4-phenylbenzoyl)acrylic acid **I** reacted with 6-(2′-methoxynaphthalenyl)-4-phenylpyrimidine-2(1H)thione to furnish α-[6-(2′-methoxynaphthalenyl)-4-phenylpyrimidinylthio]-β-(4-phenylbenzoyl)propionic acid **II**. Dehydration of acid **II** aforded furanone derivative **III**. The behaviour of **III** towards hydrazine hydrate, hydroxylamine hydrochloride, primary amines, aromatic hydrocarbons (under Friedel-Crafts conditions) and carbon nucleophiles (under Grignard conditions) has been investigated.

Key words: Michael reaction; nitrogen nucleophiles; biological evaluation.

In a continuing search for compounds exhibiting pharmacological activity, our interest was channeled into the area involving the extention of the previous studies[1,2] to prepare new related derivatives through sulphur nucleophilic addition to β-aroylacrylic acid followed by cyclization of the intermediate adduct and to screen some of the prepared compounds for antimicrobial activities.

The behaviour of β-aroylacrylic acids toward thiophenol[3] and pyridazinethione derivatives[4] have been investigated, now we report in this paper the behaviour of β-(4-phenylbenzoyl)acrylic acid **I** towards pyrimidinethione derivative. Thus, β-(4-phenylbenzoyl)acrylic acid **I** underwent 1,2-dipolar addition with 6-(2′-methoxynaphthalenyl)-4-phenylpyrimidine-2(1H) thione under Michael condition to furnish the corresponding α-[6-(2′-methoxynaphthalenyl)-4-phenylpyrimidinylthio]-β-(4-phenylbenzoyl)propionic acid (**II**). The addition of the sulphur anion occurred α to the carboxyl group in these instances, the polarization of the double bound by the keto group strongly outweighed that exhibited by the carboxyl group; the keto group giving a more stable carbonium ion than the carboxyl group, i.e. the α-carbon atom accepts the nucleophile (donor in Michael condensation) more readily than the β-carbon atom.



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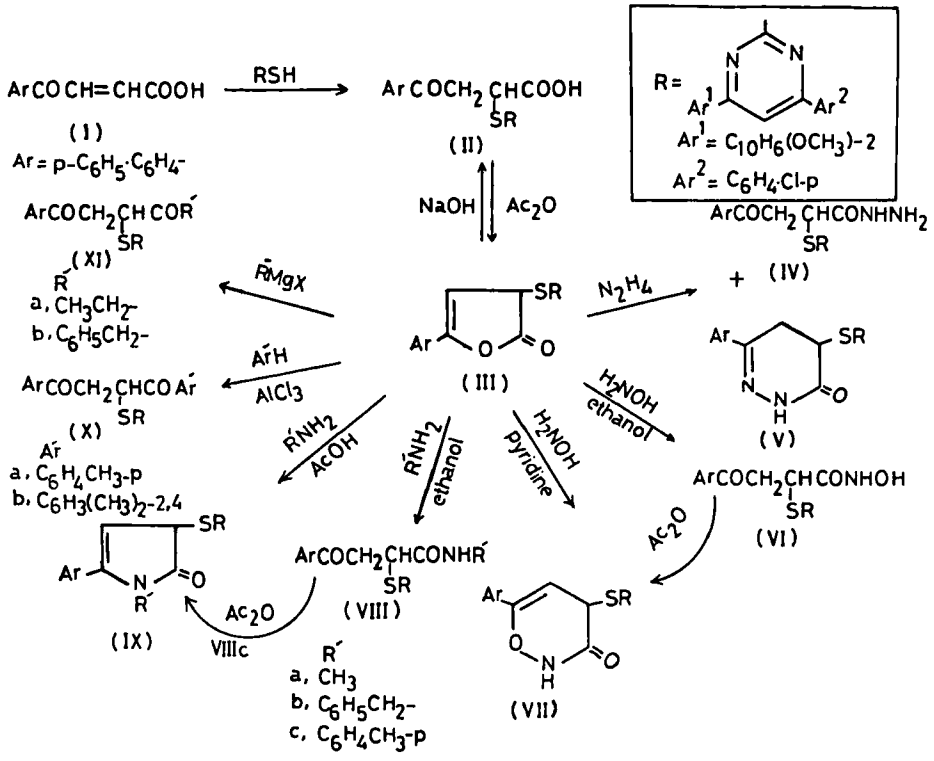
The acid **II** is easily dehydrated by boiling with acetic anhydride or by heating at its melting point to furnish α-[6-(2′-methoxynaphthalenyl)-4-phenylpyrimidinylthio]-γ-xenyl-$\Delta^{\beta,\gamma}$-butenolide[5,6] (**III**). The structure assigned for the butenolide **III** was supported from: a) Microanalytical and spectral data (cf. Exp.). b) It is insoluble in aqueous alkali on cold. c) It is readily hydrolysed by hot alkali giving the corresponding acid[7] **II**.

In continuation of our studies[1,8] on the ring opening and reactivity of furan derivatives we have carried out similar studies on butenolide **III** and the results are reported in this paper.

Butenolide **III** reacts with hydrazine hydrate in boiling ethanol to yield α-[6-(2′-methoxynaphthalenyl)-4-phenylpyrimidinylthio]-β-(4-phenylbenzoyl)propionic acid hydrazide (**IV**) together with 4-[6′-(2-methoxynaphthalenyl)-4′-phenylpyrimidinylthio]-6-xenyl-2,3,4,5-tetrahydropyridazin-3-one (**V**). Both compounds **V** and **IV** were also obtained by independent synthesis through the action of hydrazine on the acid **II**, and on its chloride.

The behaviour of **III** with hydroxylamine hydrochloride in different medium also has been studied. Thus, butenolide **III** on the reaction with hydroxylamine hydrochloride in boiling ethanol affected opening of the heterocyclic ring (acyl-oxygen cleavage) leading to the formation of 2-[6′-(2-methoxynaphthalenyl)-4′-phenylpyrimidinylthio]-3-(4′-phenylbenzoyl)propionamide (**VI**). When the reaction was carried out in boiling pyridine 4-[6′-(2-methoxynaphthalenyl)-4′-phenylpyrimidinylthio]-6-xenyl-2,4-dihydro-1,2-oxazin-3-one (**VII**) was obtained. Interestingly,



propionamide (**VI**) could be converted to oxazinone **VII** by boiling in acetic anhydride.

Reaction of **III** with amines such as methyl-, benzylamine or p-toluidine in boiling ethanol brought about the ring opening of **III** to give the corresponding 1,4-butandione derivatives **VIIIa–c**. Compound **VIIIa–c** could also be obtained through an independent synthesis by the action of methyl-, benzylamine or p-toluidine on the acid chloride of **II**. Cyclization of **VIIIc** in the presence of acetic anhydride furnished 3-[6′-(2-methoxynaphthalenyl)-4′-phenylpyrimidinylthio]-1-p-tolyl-5-xenyl-Δ^4-pyrrolin-2-one **IX**. **IX** could also be prepared via the reaction of **III** with p-toluidine in the presence of acetic acid-sodium acetate.

Recently,[1] we have reported that 3-benzylamino-5-(dibenzothien-4′-yl) furan-2-one underwent ring opening by aromatic hydrocarbons catalysed by Lewis acid. In this investigation, we agreed with this type of fission. Thus, butenolide **III** reacts with toluene or *m*-xylene in the presence of anhydrous aluminium chloride and yielded 1-(2′-methyl- or 2′,4′-dimethylphenyl)-2-[6′-(2-methoxynaphthalenyl)-4′-phenylpyrimidinylthio]-4-xenyl-1,4-butandione (**Xa, b**). Compounds **Xa, b** was also obtained by an independent synthesis via the Friedel-Craft's reaction involving the chloride of **II** and toluene or *m*-xylene. The reaction take place via Lewis acid catalysed acyl-oxygen fission to give acylium ion, which acts as acylating agent for the highly reactive aromatic hydrocarbons.

In continuation of our investigation on the ring opening reactions of butenolide **III** with some nucleophile, we report that the reaction of **III** with ethylmagnesium iodide or benzylmagnesium chloride furnished 1-(ethyl or benzyl)-2-[6′-(2-methoxynaphthalenyl)-4′-phenylpyrimidinylthio]-4-xenyl-1,4-butandione (**XIa, b**).

SCREENING FOR AN ANTIMICROBIAL ACTIVITY

The antimicrobial activity of some synthesized derivatives on different strains of various organisms were tested using the hole plate and filter paper disc methods.[9,10] The tested compounds were dissolved in 10% acetone (v/v). The concentrations were chosen as follows 125, 250 and 500 μg/ml. The results are summarized in Table I. It should be noted that the other pharmacological studies are still in progress.

EXPERIMENTAL

Melting points were determined in open capillaries and are not corrected. IR spectra in KBr were recorded on a Pye-Unicam SP_3-200 spectrophotometer. ^1H NMR were measured in DMSO on a Joel FX 90 Q 9 MHz (Fourier transform NMR spectrometer) using TMS as internal reference and chemical shifts were expressed as δ (ppm). Microanalytical data (C, H, N.) were obtained from the Microanalytical Center at Cairo University. The physical data are listed in Table II.

6-(2′-Methoxynaphthalenyl)-4-phenylpyrimidine-2(1H) thione. It was prepared by following the reported method.[11] Recrystallisation from ethanol gave yellow needles, yield 72%, m.p. 174–176°C, Anal, $C_{21}H_{16}N_2OS$. Calcd: C, 73.2; H, 4.6; N, 8.1. Found: C, 73.2; H, 4.8; N, 8.0. IR: ν_{max}; 3250–3150 (NH), 2560 (SH), 1620 (C=N), 1260 cm^{-1} (C=S).

TABLE I

Activity (A) and minimum inhibitory concentration (MIC) calculated as mmol/ml for compounds (IV–Xa)

Compd. No.	Bacillus subtilis		Bacillus cereus		Aspergillus niger		Penicillium spp.	
	A	MIC	A	MIC	A	MIC	A	MIC
IV	++	0.40×10^{-3}	+	0.20×10^{-3}	+	0.81×10^{-3}	+	0.20×10^{-3}
VII	+	0.21×10^{-3}	+	0.21×10^{-3}	-	-	+++	0.84×10^{-3}
VIIIa	+	0.20×10^{-3}	+	0.41×10^{-3}	-	-	+	0.82×10^{-3}
VIIIc	+	0.36×10^{-3}	+	0.18×10^{-3}	+	0.36×10^{-3}	-	-
IX	++	0.37×10^{-3}	+	0.18×10^{-3}	+	0.74×10^{-3}	+	0.37×10^{-3}
Xa	+	0.37×10^{-3}	+	0.37×10^{-3}	-	-	-	-

- The width of the zone of inhibition indicates the potency of antimicrobial activity .
(-) no antimicrobial activity ; (+) mild activity with the diameter of the zone equal to 0.7 cm.; (++) moderate activity with the diameter of the zone equal to 1.3 cm.; (+++) marked activity with the diameter of the zone equal to 1.7 cm.
- Origin of cultures
Botany Department, Faculty of Science, Benha University, Egypt.
- The results of control samples were not included in the table ; They show negative response .

TABLE II

Physical data of various compound prepared

Compd. No.	m.p* °C	Yield (%)	Mol. formula	Calc. (%) (Found) C	H	N
II	233-5[a]	65	$C_{37}H_{28}N_2O_4S$	74.4 (74.9	4.6 5.0	4.6 4.5)
III	188-90[d]	65	$C_{37}H_{26}N_2O_3S$	76.8 (76.4	4.4 4.8	4.8 4.5)
IV	224-6[c]	26	$C_{37}H_{30}N_4O_3S$	72.7 (72.3	4.9 5.1	9.1 9.3)
V	250-2[a]	57	$C_{37}H_{28}N_4O_2S$	75.0 (74.8	4.7 5.0	9.4 9.6)
VI	240-3[a]	60	$C_{37}H_{29}N_3O_4S$	72.6 (72.3	4.7 4.4	6.8 6.5)
VII	212-5[a]	63	$C_{37}H_{27}N_3O_3S$	74.8 (74.6	4.5 4.8	7.0 7.3)
VIIIa	280-2[a]	60	$C_{38}H_{31}N_3O_3S$	74.8 (75.0	5.0 5.9	6.8 6.8)
VIIIb	166-8[b]	55	$C_{44}H_{35}N_3O_3S$	77.0 (77.3	5.1 4.8	6.1 6.2)
VIIIc	>360[a]	40	$C_{44}H_{35}N_3O_3S$	77.0 (76.7	5.1 5.5	6.1 5.9)
IX	216-8[b]	57	$C_{44}H_{33}N_3O_2S$	79.1 (78.9	4.9 5.2	6.2 6.0)
Xa	>360[a]	50	$C_{44}H_{34}N_2O_3S$	78.8 (78.6	5.0 5.4	4.1 3.9)

TABLE II (*Continued*)

Compd. No.	m.p °C	Yield (%)	Mol. formula	Calc. (%) (Found) C	H	N
Xb	276-8[a]	52	$C_{45}H_{36}N_2O_3S$	78.9 (78.8	5.2 5.7	4.0 4.4)
XIa	158-60[a]	57	$C_{39}H_{32}N_2O_3S$	76.9 (76.7	5.2 5.1	4.6 5.0)
XIb	>360[a]	50	$C_{44}H_{34}N_2O_3S$	78.8 (79.1	5.0 4.8	4.1 4.0)

• The compounds recrystallised from (a) butanol, (b) ethanol, (c) benzene, (d) benzene-light pet. (60-80°).

α-[6-(2'-Methoxynaphthalenyl)-4-phenylpyrimidinylthio]-β-(4-phenylbenzoyl)propionic acid (**II**). A solution of **I** (0.01 mole) and the thione derivative (0.01 mole) with a few drops of piperidine in dry benzene (50 ml) was refluxed for 4 hrs. The reaction mixture was concentrated, the solid that separated after cooling was crystallised from proper solvent to give **II**; IR: ν_{max}; 3460–3150 (OH), 1720 (Carboxylic CO), 1685 cm^{-1} (Ketonic CO). ^1H NMR: δ = 2.9–3.6 (m, 2H, non-equivalent —CH_2—); 3.9 (s, 3H, —OCH_3); 4.8 (q, 1H, >CH—); 6.8–7.8 (m, 21H, Ar—H).

α-[6-(2'-Methoxynaphthalenyl)-4-phenylpyrimidinylthio]-γ-xenyl-$\Delta^{\beta,\gamma}$-butenolide (**III**).

Method A: A solution of appropriate acid **II** (0.01 mole) in acetic anhydride (30 ml) was refluxed for 2 hr. The solid obtained after concentration and cooling was crystallised from a suitable solvent to give the butenolide **III**.

Method B: The acid **II** was heated at its melting point for half an hour and the solid crystallized from a suitable solvent to furnish **III** which was compared with that obtained above; IR: ν_{max}; 1770 (γ-Lactonic CO), 1600 cm^{-1} (C=C). ^1H NMR: δ = 3.6 (s, 1H, CH_3—); 3.9 (s, 3H, —OCH_3); 6.8–7.6 (m, 22H, olefinic and aromatic protons).

Alkaline hydrolysis of **III**: *Formation of* **II**. A solution of **III** (0.01 mole) in (20 ml) sodium hydroxide solution (10%) was refluxed for 2 hr. and then poured into ice-HCl mixture. The crude product obtained was crystallized from *n*-butanol to give the product proved to be **II** by melting point and mixed melting point determinations.

Action of hydrazine hydrate on the butenolide **III**: *Formation of* **IV** *and* **V**. A solution of **III** (0.01 mole) and hydrazine hydrate (0.03 mole) in ethanol (60 ml) was heated under reflux for 4 hrs. The product that separated on concentration and cooling was filtered off and fractionally crystallized from benzene to give the hydrazide **IV**. The benzene insoluble part was crystallized from *n*-butanol and identified as the pyridazinone **V** (cf. Table II). IR of **IV** and **V**: ν_{max}; 3400–3300 (NH), 1670 (amidic CO). In addition to the above bands, **IV** exhibited band at 1685 cm^{-1} (Ketonic CO).

Independent synthesis of hydrazide **IV**. An ethereal solution of the acid chloride of **II** (0.01 mole) was treated by hydrazine hydrate (0.01 mole). The mixture was shaken well for half an hour and then heated on a steam bath for another half an hour. The ether was evaporated and the residue was poured into water, the solid separated filtered of and recrystallized from benzene to give a product identified as **IV** by m.p. and m.m.p. determinations.

Independent synthesis of pyridazinone **V**. A mixture of the acid **II** (0.01 mole) and hydrazine hydrate (0.01 mole) was refluxed in ethanol for 7 hrs. The solid that separated after concentration and cooling was crystallized from *n*-butanol to yield a product identified as V by m.p. and m.m.p. determinations.

Condensation of **III** *with hydroxylamine hydrochloride: Formation of* **VI** *and* **VII**. A solution of **III** (0.01 mole), hydroxylamine hydrochloride (0.01 mole) and ethanol or pyridine (20 ml) was refluxed for 4 hrs. The solid product obtained after crystallization was found to be the corresponding propion-

amide **VI** or oxazinone **VII**, respectively. (cf. Table II), IR of **VI**: ν_{max}; 3450–3200 (OH and NH), 1680 (Ketonic CO), 1660 (amidic CO), while the IR of **VII**: ν_{max}; 3370–3200 (OH and NH), 1695 (amidic CO), 1635 cm^{-1} (C=N).

Action of acetic anhydride on **VI**: *Formation of* **VII**. A solution of **VI** (1 gm) in (30 ml) acetic anhydride was refluxed for 2 hr. The solid obtained after concentration and cooling was crystallized from the proper solvent to yield a product identified as **VII** by m.p. and m.m.p. determinations.

Reaction of the butenolide **III** *with amines in alcohol: Formation of* **VIIIa–c**. To a solution of **III** (0.01 mole) in ethanol (20 ml), methyl-, benzylamine or p-toluidine (0.015 mole) was added and the mixture refluxed for 6 hrs. The solid that separated on cooling was crystallized from a suitable solvent to furnish the corresponding **VIIIa–c**, IR: ν_{max}; 3350–3200 (NH), 1685–1660 cm^{-1} (Ketonic and amidic CO).

Independent synthesis of **VIIIa–c**. An ethereal solution of the acid chloride of **II** (0.01 mole) was added to an ethereal solution of methyl-, benzylamine or p-toluidine (0.015) and then heated on a steam bath for one hour. Evapouration of the excess ether and then addition of the reaction mixture onto water gave a solid substance that was crystallized from a suitable solvent and identified to be **VIIIa–c** by m.p. and m.m.p. determinations.

Action of acetic anhydride on **VIIIc**: *Formation of* **IX**. A solution of **VIIIc** (1 g) in (30 ml) acetic anhydride was heated on a steam-bath for 4 hr. The solid obtained after concentration and cooling was crystallized from the proper solvent to furnish **IX**, IR: ν_{max}; around 1700 (amidic CO), 1620 cm^{-1} (C=C). ^1H NMR: δ = 2.4 (s, 3H, Ar—CH_3); 3.7 (s, 3H, —OCH_3); 4.1 (s, 1H, Cyclic CH_3); 6.8–7.9 (m, 25H, olefinic and aromatic protons).

Reaction of the butenolide **III** *with p-toluidine in ACOH/ACON$_a$: Formation of* **IX**. A mixture of **III** (0.01 mole), p-toluidine (0.01 mole) and sodium acetate (0.02 mole) in acetic acid (40 ml) was heated under reflux for 10 hrs. The mixture was poured into ice-water and the solid separated was crystallized from the proper solvent to yield a product identified as **IX** by m.p. and m.m.p. determinations.

Reaction of **III** *with aromatic hydrocarbons under Friedel-Craft's conditions: Formation of* **Xa, b**. A solution of butenolide **III** (0.01 mole) in toluene or *m*-xylene was gradually added to a suspension of anhydrous aluminium chloride (0.04 mole) in 100 ml of the same aromatic solvent. The suspension was stirred at room temperature for 10 hr. The whole mixture was then added to HCl-ice and the excess of the solvent was then removed by steam distillation. The solid separated was crystallized from the proper solvent to give the dione **Xa, b**, IR: ν_{max}; 1690–1670 cm^{-1} (two Ketonic CO). ^1H NMR of **Xb** δ = 2.36 and 2.5 (s, 6H, Ar—CH_3); 3.5 (s, 3H, —OCH_3); 3.8–4.3 (m, 2H, non-equivalent —CH_2—CH<); 4.6–4.9 (q, 1H, CH_2CH<); 6.8–7.6 (m, 23H, Ar—H).

Independent synthesis of **Xa, b**. A solution of **II** (0.01 mole) and thionylchloride (0.04 mole) was refluxed for two hours, and the excess of thionylchloride was removed by distillation under reduced pressure. The resulting acid chloride was treated with toluene or *m*-xylene (50 ml) and anhydrous aluminium chloride was added portionwise in a period of half an hour to a stirred solution. Heating was continued for two hours on a steam bath, the reaction mixture was left overnight and then the whole was added to ice-HCl. The organic layer was washed with water and the excess solvent was removed by steam distillation. The solid separated was crystallized from the proper solvent to furnish a product which could be identified as **Xa, b** by m.p. and m.m.p. determinations (cf. Table II).

Reaction of **III** *with Grignard reagents: Formation of* **XIa, b**. To (0.15 mole) of magnesium turnings in 100 ml of dry ether was added dropwise (0.15 mole) of ethyl iodide or benzylchloride. After the reaction had subsided, the furanone **III** (0.01 mole) dissolved in 100 ml of dry benzene was added in portions over one hour period. The mixture was heated under reflux for an additional 6 hr. and then work up as usual[8] to afford **XIa, b**, IR: ν_{max}; 1695–1660 cm^{-1} (two Ketonic CO).

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