

Synthesis and Some Reactions of Ethyl 4-(2,3-Diphenyl-5-methoxybenzofuran-6-yl)- and 4-(2,3-Diphenyl-6-methoxybenzofuran-5-yl)-2,4-diketobutanoates

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Ethyl 4-(2,3-diphenyl-5-methoxybenzofuran-6-yl)- (*Ib*) and 4-(2,3-diphenyl-6-methoxybenzofuran-5-yl)-2,4-diketobutanoates (*IIf*) are prepared by Claisen condensation of 6-acetyl-5-methoxy- and 5-acetyl-6-methoxy-2,3-diphenylbenzofuran, respectively, with ethyl oxalate. The esters *Ib* and *IIf* reacted with hydrazine hydrate and semicarbazide chloride to give the corresponding pyrazoles. The corresponding isoxazoles are prepared by the reaction of *Ib* and *IIf* with hydroxylammonium chloride. On reaction with different amines, compounds *Ib* and *IIf* yielded the corresponding amides. When compounds *Ib* and *IIf* were coupled with aromatic diazonium compounds, they yielded the mixed azo compounds. A pyrazole derivative on reaction with benzylamine gave the corresponding amide which was prepared also *via* the reaction of an amine with hydrazine hydrate.

Because of the wide spread of benzofuran derivatives in the field of medicinal chemistry [1–3] this work deals with the synthesis of some new compounds in this series with the aim of biological evaluation.

Claisen condensation of 6-acetyl-5-methoxy- (*Ia*) and 5-acetyl-6-methoxy-2,3-diphenylbenzofuran (*IIfa*) [4] with ethyl oxalate in the presence of sodium metal

gave the esters ethyl 4-(2,3-diphenyl-5-methoxybenzofuran-6-yl)- (*Ib*) (Table 1) and 4-(2,3-diphenyl-6-methoxybenzofuran-5-yl)-2,4-dioxobutanoates (*IIf*), respectively.

The esters *Ib* and *IIf* reacted with hydrazine hydrate in acetic acid to yield ethyl 3-(2,3-diphenyl-5-methoxybenzofuran-6-yl)- (*IIIa*) and ethyl 3-(2,3-

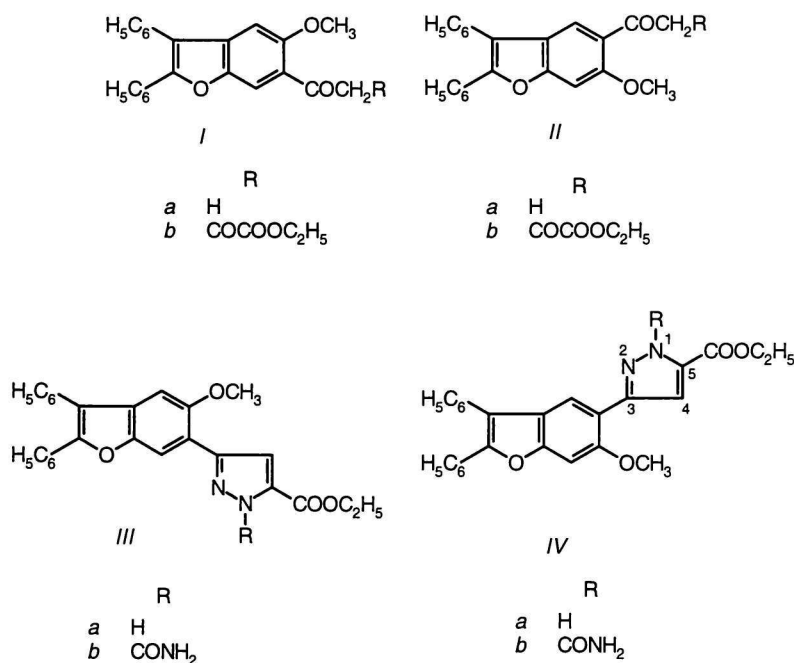
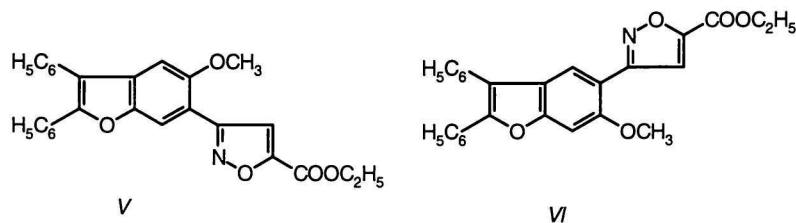


Table 1. Characterization of the Prepared Compounds

Compound	Formula	w_i (calc.)/% w_i (found)/%			Yield/%	M.p./°C
		C	H	N		
<i>Ib</i>	C ₂₇ H ₂₂ O ₆	73.30	4.98		70	145
	442.47	73.10	4.65			
<i>IIb</i>	C ₂₇ H ₂₂ O ₆	73.30	4.98	—	60	155
	442.47	73.80	4.80	—		
<i>IIIa</i>	C ₂₇ H ₂₂ N ₂ O ₄	73.97	5.02	6.39	80	155
	438.48	73.80	4.90	6.10		
<i>IIIb</i>	C ₂₈ H ₂₃ N ₃ O ₅	69.85	4.78	8.73	75	120
	481.51	69.60	4.30	8.60		
<i>IVa</i>	C ₂₇ H ₂₂ N ₂ O ₄	73.97	5.02	6.39	80	184
	438.48	73.64	5.01	5.95		
<i>IVb</i>	C ₂₈ H ₂₃ N ₃ O ₅	69.85	4.78	8.73	75	190
	481.51	69.34	4.76	8.45		
<i>V</i>	C ₂₇ H ₂₁ NO ₅	73.80	4.78	3.19	70	228
	439.47	73.52	4.40	3.01		
<i>VI</i>	C ₂₇ H ₂₁ NO ₅	73.80	4.78	3.19	70	230
	439.47	73.30	4.50	2.90		
<i>VIIa</i>	C ₃₂ H ₂₅ NO ₅	76.34	4.97	2.78	80	213
	503.55	76.95	4.83	2.45		
<i>VIIb</i>	C ₂₉ H ₂₅ NO ₆	72.05	5.18	2.89	80	200
	483.52	71.90	4.85	2.45		
<i>VIIc</i>	C ₃₂ H ₂₅ NO ₅	76.34	4.97	2.78	75	198
	503.55	76.01	4.80	2.60		
<i>VIIIa</i>	C ₃₂ H ₂₅ NO ₅	76.34	4.97	2.78	75	182
	503.55	76.20	4.70	2.60		
<i>VIIIb</i>	C ₂₉ H ₂₅ NO ₆	72.05	5.18	2.89	85	173
	483.52	72.00	4.95	2.70		
<i>VIIIc</i>	C ₃₂ H ₂₅ NO ₅	76.34	4.97	2.78	85	176
	503.55	76.37	4.69	2.90		
<i>IXa</i>	C ₃₃ H ₂₆ N ₂ O ₆	72.53	4.76	5.13	70	167
	546.58	72.80	4.80	5.10		
<i>IXb</i>	C ₃₄ H ₂₈ N ₂ O ₆	72.86	5.00	5.00	70	174
	560.61	72.56	4.75	4.60		
<i>Xa</i>	C ₃₃ H ₂₆ N ₂ O ₆	72.53	4.76	5.13	75	183
	546.58	72.30	4.50	4.90		
<i>Xb</i>	C ₃₄ H ₂₈ N ₂ O ₆	72.86	5.00	5.00	75	188
	560.61	72.60	4.80	5.00		
<i>XI</i>	C ₃₂ H ₂₅ N ₃ O ₃	76.95	5.01	8.42	75	175
	499.57	76.40	4.90	7.90		



diphenyl-6-methoxybenzofuran-5-yl)-pyrazole-5-carboxylate (*IVa*), respectively.

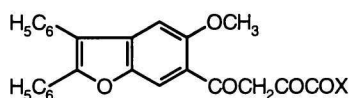
The reaction of compounds *Ib* and *IIb* with semicarbazide chloride led to the formation of the corresponding pyrazole derivatives *IIIb* and *IVb*, respectively.

Ethyl 3-(2,3-diphenyl-5-methoxybenzofuran-6-yl)-pyrazole-5-carboxylate (*V*) and ethyl 3-(2,3-diphenyl-6-methoxybenzofuran-5-yl)isoxazole-5-carboxylate (*VI*) were furnished by

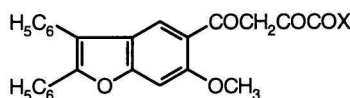
the reaction of *Ib* and *IIb* with hydroxylammonium chloride, respectively.

IR spectrum of compound *V* was in agreement with the proposed structure which showed bands of the C=N and ester groups at 1640 cm⁻¹ and 1725 cm⁻¹, respectively.

The esters *Ib* and *IIb* reacted with amines, namely benzylamine, morpholine or *p*-toluidine to yield the corresponding amides *VIIa*—*VIIc* and *VIIIa*—*VIIIc*,

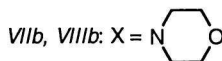


VII

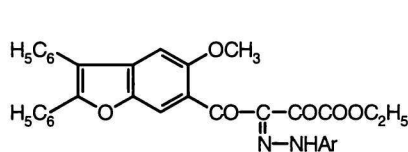


VIII

VIIa, VIIIa: X = NHCH₂C₆H₅

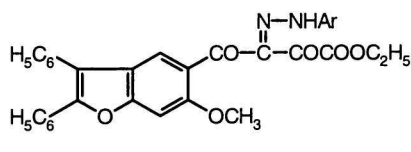


VIIc, VIIIc: X = NH—C₆H₄CH₃-p



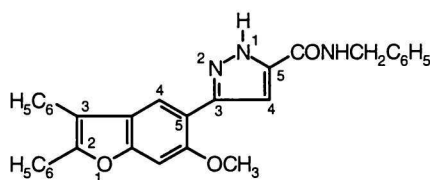
IX

Ar
 a C₆H₅
 b C₆H₄CH₃-p



X

Ar
 a C₆H₅
 b C₆H₄CH₃-p



XI

respectively.

IR spectrum of compound *VIIIa* showed the presence of amide group at $\bar{\nu} = 1670 \text{ cm}^{-1}$ and absence of ester group.

It has been reported that α -keto esters on reaction with diazonium salts yielded the corresponding aryl hydrazones with cleavage of the ethoxalyl group [5, 6]. In this investigation, when compounds *Ib* and *IIb* were coupled with aromatic diazonium compounds in the presence of sodium acetate, it yielded hydrazones *IXa*, *IXb* and *Xa*, *Xb*, respectively.

IR spectrum of compound *IXa* favoured the hydrazone structure, it showed bands at 1640 cm^{-1} and 1620 cm^{-1} due to conjugated and intramolecular hydrogen-bonded ketonic carbonyl groups, respectively [7, 8]. The band at 1540 cm^{-1} was attributed to C=N group in conjugation with carbonyl group [8]. The spectrum showed also a band at 1750 cm^{-1} which is characteristic of ester group.

The reaction of ethyl 3-(2,3-diphenyl-6-methoxybenzofuran-5-yl)pyrazole-5-carboxylate (*IVa*) with benzylamine gave the corresponding amide *XI*. Compound *XI* was also obtained *via* the reaction of the

amide *VIIIa* with hydrazine hydrate in acetic acid.

IR spectrum of compound *XI* revealed the absence of the ester group and presence of amide group at $\bar{\nu} = 1670 \text{ cm}^{-1}$.

EXPERIMENTAL

Melting points are not corrected. The IR spectra were recorded on a Unicam infrared spectrophotometer, Model SP 2000 in KBr. ¹H NMR spectra were run in CDCl₃ at 60 MHz, with TMS as internal standard on a Varian instrument.

2,4-Dioxobutanoate Derivatives *Ib* and *IIb*

A solution of *Ia* or *IIa* (4 g) in ethyl oxalate (50 cm³) was slowly added to powdered sodium metal (4 g). When the initial vigorous reaction subsided, the reaction mixture was refluxed for 5 h and then left to cool. Methanol (5 cm³) was added to destroy any excess of sodium metal. The reaction mixture was diluted with water, then acidified with acetic acid and the solid that separated was filtered off, recrystallized

from ethanol to give *Ib* or *IIb* as yellow crystals.

Ib, IR spectrum, $\bar{\nu}/\text{cm}^{-1}$: 1630 (β -diketone group), 1750 (α -keto ester group) [9]. *IIb*, IR spectrum, $\bar{\nu}/\text{cm}^{-1}$: 1630 (β -diketone group), 1740 (α -keto ester group). ^1H NMR spectrum, δ : 7.75 (s, 1H, C-4—H), 7.05—7.35 (m, 10H, 2 C₆H₅), 6.90 (s, 1H, C-7—H), 6.60 (s, 1H, enol—CH=), 4.35 (q, 2H, OCH₂CH₃), 3.90 (s, 3H, OCH₃), 1.45 (t, 3H, OCH₂CH₃).

Ethyl Pyrazole-5-carboxylate Derivatives *IIIa* and *IVa*

A mixture of *Ib* or *IIb* (0.5 g) and hydrazine hydrate (0.5 cm³) in acetic acid (10 cm³) was refluxed for 5 h, diluted with water and left to cool, and the solid obtained was recrystallized from ethanol.

IIIa, *IVa*, IR spectra, $\bar{\nu}/\text{cm}^{-1}$: 1620 (C=N), 1725 (ester group). *IVa*, ^1H NMR spectrum, δ : 7.35 (s, 1H, benzofuran C-4—H), 6.80—7.30 (m, 11H, 2 C₆H₅, pyrazole C-4—H), 6.80 (s, 1H, C-7—H), 4.25 (q, 2H, OCH₂CH₃), 1.35 (t, 3H, OCH₂CH₃).

Ethyl 1-Carbamoylpyrazole-5-carboxylate Derivatives *IIIb* and *IVb*

A solution of *Ib* or *IIb* (4 mmol) in the minimum amount of ethanol was added to a solution of semicarbazide (7 mmol) in the minimum amount of water. The reaction mixture was refluxed for 3 h and then left to cool, and the solid that separated was recrystallized from ethanol as white crystals.

IVb, IR spectrum, $\bar{\nu}/\text{cm}^{-1}$: 1630 (C=N), 1670 (CoNH₂), 1730 (ester group). ^1H NMR spectrum, δ : 7.35 (s, 1H, benzofuran C-4—H), 6.90—7.20 (m, 11H, 2 C₆H₅, pyrazole C-4—H), 6.85 (s, 1H, C-7), 4.20 (q, 2H, OCH₂CH₃), 3.85 (s, 3H, OCH₃), 1.30 (t, 3H, OCH₂CH₃).

Ethyl Isoxazole-5-carboxylate Derivatives *V* and *VI*

A mixture of *Ib* or *IIb* (0.5 g), hydroxylammonium chloride (0.5 g), and few drops of pyridine in ethanol (20 cm³) was refluxed for 3 h, then left to cool. The solid that separated was recrystallized from ethanol as yellow crystals.

Amides *VIIa*—*VIIc* and *VIIIa*—*VIIIc*

A mixture of *Ib* or *IIb* (1 g) and the appropriate amine (3.3 cm³) in ethanol (20 cm³) was refluxed for 8 h (the solution became yellow), then left to cool. The solid that separated was recrystallized from ethanol as white to yellow crystals.

2,3,4-Triketobutanoate-3-arylhydrazones *IXa*, *IXb* and *Xa*, *Xb*

To a solution of sodium acetate (1.2 g) dissolved in the least amount of water, *Ib* or *IIb* (1.2 g) dissolved in ethanol (20 cm³) was added and stirred vigorously. A freshly prepared diazonium chloride solution (prepared from 5 mmol of the appropriate amine in 1.25 cm³ of concentrated hydrochloric acid and 0.9 cm³ of water) diazotized with 5 mmol of sodium nitrite, dissolved in the least amount of water, was slowly added dropwise while stirring and cooling. The stirring was continued for another 30 min, then the reaction mixture was filtered and the reddish solid obtained was recrystallized from ethanol.

Xa, ^1H NMR spectrum, δ : 7.60 (s, 1H, C-4—H), 6.80—7.45 (m, 15H, 3 C₆H₅), 6.70 (s, 1H, C-7—H), 4.20 (q, 2H, OCH₂CH₃), 3.85 (s, 3H, OCH₃), 1.30 (t, 3H, OCH₂CH₃).

Xb, ^1H NMR spectrum, δ : 7.65 (s, 1H, C-4—H), 6.75—7.45 (m, 14H, 2 C₆H₅, C₆H₄), 6.75 (s, 1H, C-7—H), 4.25 (q, 2H, OCH₂CH₃), 3.85 (s, 3H, OCH₃), 2.1 (s, 3H, CH₃), 1.35 (t, 3H, OCH₂CH₃).

3-(2,3-Diphenyl-6-methoxybenzofuran-5-yl)-5-(*N*-benzylcarbamoylpyrazole) (*XI*)

In a similar manner as in case of *VII* and *VIII*, *IVb* (1 g) on reaction with benzylamine gave compound *XI* as white crystals (from ethanol).

Compound *XI* was also obtained *via* the reaction of *VIIIb* (0.5 g) with hydrazine hydrate (0.5 cm³) in acetic acid (10 cm³), in a similar manner as in case of *III* and *IV*.

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