REACTIONS OF BENZOYLISOTHIOCYANATE WITH ACETOACETANILIDE: SYNTHESIS OF PYRAZOLE, PYRIDINE, PYRIMIDINE, PYRAZOLO[3,4-*d*]-PYRIMIDINE, PYRAZOLO[4,3-*d*]PYRIMIDINE AND PYRIDO[4,3-*d*]OXAZINE DERIVATIVES

Rafat Milad MOHAREB[a], Suzan Ibrahim AZIZ[a], Nadia Iskander ABDEL-SAYED[b] and Fawzia Zakeria EL-ABLACK[c]

[a] *Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt*
[b] *Chemistry Department, College for Girls, Ain Shams University, Heliopolis, Cairo, Egypt*
[c] *Chemistry Department, Damiete Faculty of Science, Mansoura University, Damiete, Egypt*

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Compounds containing –N–C(R)=X moiety (X = O, S) are of biological interest as bacterial[1], fungicidal[2] and antiviral[3] agents. In addition, their anesthetic activities have also been discussed[4]. Recently we were involved in a program aiming at developing new efficient procedures for the synthesis of such reagents[5 – 9]. As a continuation of our work, we describe in this article the results of investigations involving the reaction of benzoyl isothiocyanate *I* with acetoacetanilides *IIa*, *IIb*.

EXPERIMENTAL

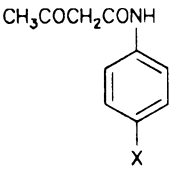
All melting points are uncorrected. Infrared spectra were recorded on Perkin–Elmer SP 177 spectrometer in KBr disc (wavenumbers in cm^{-1}). NMR spectra were taken on Varian A-300 (300 MHz) instrument at 25 °C in CD_3SOCD_3 with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale) coupling constants (*J*) in Hz.

Benzoyl Isothiocyanate (*I*)

To a solution of benzyl chloride (14 g, 0.1 mol) in dry acetone (50 ml) ammonium thiocyanate (7.8 g, 0.1 mol) was added and reaction mixture boiled for 15 min. Physico-chemical data and spectra of synthesized compounds are presented in Tables I and II, respectively.

3-Benzoylaminothiocarbonyl-3-phenylformamido-2-propanone (*IIIa*) and 3-Benzoylamino-thiocarbonyl-3-(4'-methylphenyl)formamido-2-propanone (*IIIb*); General Procedure

To a suspension of sodium salt of *IIa* or *IIb* prepared by addition of sodium metal (2.3 g, 0.1 mol) to a solution of *IIa* (1.7 g, 0.1 mol) or *IIb* (1.9 g, 0.1 mol), respectively, in dry diethyl ether (50 ml), benzoyl isothiocyanate (7.8 g, 0.1 mol) was added. The reaction mixture was left at room temperature overnight



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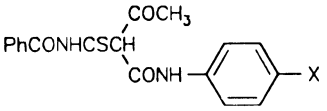

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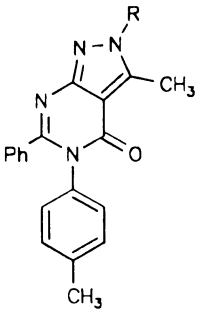

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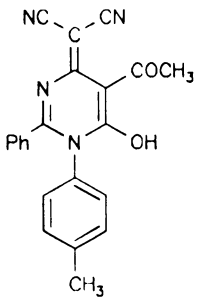

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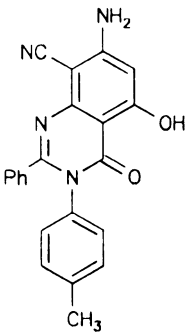

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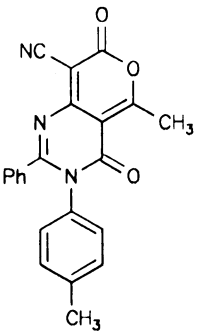

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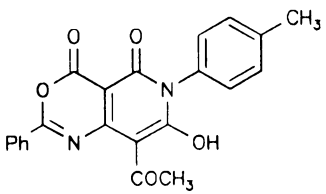
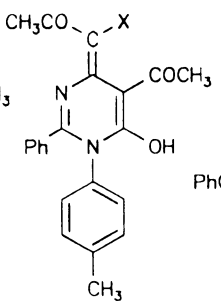
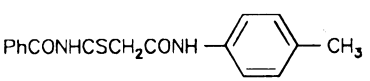


VIII



IX

IXa, X = $COCH_3$
IXb, X = COOEt



X

with stirring. The yellow gel product obtained was treated with water (20 ml) containing few drops of concentrated hydrochloric acid, and the oily material thus separated was extracted by ethyl acetate (3 × 60 ml). The product obtained after evaporation in vacuo was triturated with diethyl ether and collected by filtration.

6-Methyl-1-(4′-methylphenyl)-7-oxo-2-phenylpyrazolo[3,4-*d*]pyrimidine (*IVa*) and 2,5-Diphenyl-1-(4′-methylphenyl)-6-methyl-7-oxopyrazolo[3,4-*d*]pyrimidine (*IVb*); General Procedure

To a solution of *IIIb* (3.5 g, 0.01 mol) in ethanol (20 ml), hydrazine hydrate (0.5 g, 0.01 mol) or phenyl hydrazine (1.1 g, 0.01 mol) was added and the reaction mixture was heated under reflux for 2 h, then evaporated in vacuo. The remaining product was triturated with ethanol and collected by filtration.

5-Acetyl-6-hydroxy-1-(4′-methylphenyl)-2-phenyl-6-dicyanomethylenepyrimidine (*V*)

To a solution of *IIIb* (3.5 g, 0.01 mol) in absolute ethanol (30 ml) containing a catalytic amount of piperidine (0.5 ml), malononitrile (0.7 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 h, then evaporated in vacuo. The remaining product was triturated with diethyl ether and collected by filtration.

5-Amino-4-cyano-7-hydroxy-8-oxo-2-phenyl-1-(4′-methylphenyl)benzo[*d*]pyrimidine (*VI*)

A suspension of *V* (3.6 g, 0.01 mol) in sodium ethoxide (0.01 mol) was heated under reflux for 4 h. The solid product, formed upon pouring into water containing hydrochloric acid (pH 6), was collected by filtration.

4-Cyano-5,8-dioxo-7-methyl-2-phenyl-1-(4′-methylphenyl)pyrano[4,3-*d*]pyrimidine (*VII*)

To a solution of (3.5 g, 0.01 mol) in dioxane (30 ml) containing a catalytic amount of piperidine (0.5 ml), ethyl cyanoacetate (1.13 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 6 h, then evaporated in vacuo. The remaining product was triturated with ethanol and collected by filtration.

4-Acetyl-7,8-dioxo-5-hydroxy-2-phenyl-6-(4′-methylphenyl)pyrido[4,3-*d*]-1,3-oxazine (*VIII*)

To a solution of *IIIb* (3.5 g, 0.01 mol) in dimethylformamide (30 ml) containing piperidine (0.5 ml), diethyl malonate (1.6 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 h, then left to cool. The solid product formed upon dilution with water containing few drops of hydrochloric acid was collected by filtration.

5-Acetyl-4-(diacetylmethylenyl)-6-hydroxy-2-phenyl-1-(4′-methylphenyl)pyrimidine (*IXa*) and 5-Acetyl-4-(acetylethoxycarbonylmethylenyl)-6-hydroxy-2-phenyl-1-(4′-methylphenyl)pyrimidine *IXb*; General Procedure

To a solution of *IIIb* (3.4 g, 0.01 mol) in absolute ethanol (30 ml) containing a catalytic amount of piperidine (0.5 ml), acetyl acetone (1 ml, 0.01 mol) or ethyl acetoacetate (1.3 g, 0.01 mol) was added. The reaction mixture in each case was heated under reflux for 6 h, then evaporated in vacuo. The remaining product was triturated with dry ether and collected by filtration.

2-Benzoylaminothioxo-N-(4′-methylphenyl)acetamide (*X*)

A solution of *IIIb* (3.4 g, 0.01 mol) in absolute ethanol (50 ml) was heated under reflux for 10 h, then evaporated in vacuo. The remaining product was triturated with diethyl ether and collected by filtration.

TABLE I
Physico-chemical data of synthesized compounds

Compound	M. p., °C Solvent	Yield, g (%)	Formula (M. w.)	Calculated/Found			
				% C	% H	% N	% S
IIIa	110	25.5	$C_{18}H_{16}N_2O_3S$	63.51	4.73	8.28	9.41
	ethanol	(75)	(340.4)	63.31	4.40	8.03	9.31
IIIb	155	28.3	$C_{19}H_{18}N_2O_3S$	64.39	5.11	7.91	9.04
	ethanol	(80)	(354.4)	64.23	5.01	7.81	9.39
IVa	150	1.9	$C_{19}H_{16}N_4O$	72.14	5.10	17.71	
	ethanol	(50)	(316.4)	72.04	4.82	17.48	
IVb	168	2.6	$C_{25}H_{20}N_4O$	76.51	5.14	14.28	
	ethanol	(65)	(392.5)	76.44	5.34	14.27	
V	185	2.2	$C_{22}H_{16}N_4O_2$	71.72	4.37	15.21	
	dioxane	(63)	(368.4)	71.59	4.33	15.06	
VI	266 – 268	1.8	$C_{22}H_{16}N_4O_2$	71.72	4.37	15.21	
	DMF	(50)	(368.4)	71.64	4.42	14.99	
VII	240 – 244	2.5	$C_{22}H_{15}N_3O_3$	71.53	4.09	11.39	
	dioxane	(70)	(369.4)	71.38	4.21	11.06	
VIII	162	2.6	$C_{22}H_{16}N_2O_5$	68.03	4.15	7.21	
	dioxane	(70)	(388.4)	67.59	4.28	7.04	
IXa	248 – 250	1.8	$C_{24}H_{22}N_2O_4$	71.64	5.51	6.96	
	dioxane	(72)	(402.4)	71.39	5.37	7.09	
IXb	150 – 153	2.7	$C_{25}H_{24}N_2O_5$	69.44	5.59	6.48	
	dioxane	(63)	(432.4)	69.25	5.34	6.17	
X	150	2.4	$C_{17}H_{16}N_2O_2S$	65.36	5.16	8.96	10.26
	ethanol	(80)	(312.4)	65.21	5.08	9.15	9.94
XI	165 – 167	3.0	$C_{23}H_{18}N_4OS$	69.34	4.55	14.06	8.05
	dioxane	(78)	(398.5)	69.08	4.32	14.19	7.84
XII	300	2.1	$C_{20}H_{16}N_4O_2$	69.75	4.68	16.27	
	DMF	(63)	(344.4)	69.47	4.55	16.37	
XIII	271 – 273	2.3	$C_{20}H_{15}N_3O_3$	69.54	4.37	12.16	
	DMF	(70)	(345.4)	69.69	4.06	12.48	
XIVa	170	1.6	$C_{17}H_{16}N_4O$	69.83	5.51	19.16	
	ethanol	(58)	(292.3)	69.55	5.38	19.08	
XIVb	265 – 267	1.5	$C_{23}H_{20}N_4O$	74.98	5.47	15.21	
	ethanol	(58)	(368.4)	74.63	5.35	15.31	

TABLE II
Spectral data of synthesized compounds

Compound	IR, cm^{-1}	^1H NMR, δ(ppm)
IIIa	3 450 – 3 320 (NH); 1 710, 1 690 (3 C=O); 1 200 – 1 190 (C=S)	1.68 s, 3 H (CH_3); 4.55 s, 1 H (CH); 7.20 – 7.38 m, 10 H (2 × C_6H_5); 8.90, 10.14 2s, 2 H (2 × NH)
IIIb	3 470 – 3 320 (NH); 1 710, 1 690, 1 680 (3 C=O); 1 210 – 1 195 (C=S)	1.40, 1.68 2s, 6 H (2 × CH_3); 4.80 s, 1 H (CH); 7.30 – 7.56 m, 9 H (C_6H_5, C_6H_4); 8.89, 10.12 2s 2 H (2 × NH)
IVa	1 680 (C=O); 1 660, 1 630 (C=N, C=C)	1.50, 1.67 2s, 6 H (2 × CH_3); 7.29 – 7.53 m, 9 H (C_6H_5, C_6H_4); 8.98 s, br, 1 H (NH)
IVb	1 700 (C=O); 1 655, 1 632 (C=N, C=C)	1.54, 1.69 2s, 6 H (2 × CH_3); 7.30 – 7.53 m, 14 H (2 × C_6H_5, C_6H_4)
V	3 600 – 3 480 (OH); 2 225, 2 215 (2 CN); 1 715 (C=O)	1.40, 1.69 2s, 6 H (2 × CH_3); 7.28 – 7.49 m, 9 H (C_6H_5, C_6H_4); 10.23 s, br, 1 H (OH)
VI	3 580 – 3 320 (OH, NH_2); 2 220 (CN); 1 700 (C=O)	1.68 s, 3 H (CH_3); 4.89 s, 2 H (NH_2); 7.24 – 7.35 m, 10 H (C_6H_5, C_6H_4, benzene H-3); 10.21 s, 1 H (OH)
VII	2 220 (CN); 1 720, 1 695 (2 C=O); 1 650, 1 630 (C=N, C=C)	1.40, 1.69 2s, 6 H (2 × CH_3); 7.29 – 7.39 m, 9 H (C_6H_5, C_6H_4)
VIII	3 620 – 3 530 (OH); 1 720 – 1 700, 1 690 (3 C=O)	1.48, 1.65 2s, 6 H (2 × CH_3); 7.25 – 7.36 m, 9 H (C_6H_5, C_6H_4); 9.43 s, br, 1 H (OH)
IXa	3 620 – 3 530 (OH); 1 720 – 1 700, 1 690 (3 C=O)	1.48, 1.65 2s, 6 H (2 × CH_3); 7.25 – 7.36 m, 9 H (C_6H_5, C_6H_4); 9.43 s, br, 1 H (OH)
IXb	3 620 – 3 530 (OH); 1 700, 1 690, 1 685 (3 C=O)	1.48, 1.51, 1.69 3s, 9 H (3 × CH_3); 1.98 t, 3 H (CH_3); 4.35 q, 2 H (CH_2); 7.35 – 7.40 m, 9 H (C_6H_5, C_6H_4); 9.12 s, br, 1 H (OH)
X	3 450 – 3 320 (2 NH); 1 720, 1 700 (2 C=O)	1.69 s, 3 H (CH_3); 3.48 s, 2 H (CH_2); 7.28 – 7.31 m, 9 H (C_6H_5, C_6H_4); 8.89, 9.54 2s, 2 H (2 × NH)
XI	3 450 – 3 320 (NH); 1 710 (C=O)	1.62 s, 3 H (CH_3); 7.31 – 7.46 m, 14 H (2 × C_6H_5, C_6H_4); 9.43 s, 1 H (NH)
XII	3 450 – 3 350 (NH_2, NH); 2 220 (CN); 1 710, 1 680 (2 C=O)	1.70 s, 3 H (CH_3); 4.84 s, 2 H (NH_2); 7.01 s, 1 H (pyridine CH); 7.30 – 7.37 m, 9 H (C_6H_5); 8.95 s, 1 H (NH)
XIII	3 600 – 3 520 (OH); 3 450 – 3 320 (NH); 2 220 (CN); 1 710, 1 700 (2 C=O)	1.67 s, 3 H (CH_3); 7.01 s, 1 H (pyridine CH); 7.28 – 7.39 m, 9 H (C_6H_5, C_6H_4); 8.45 s, 1 H (NH); 10.21 s, br, 1 H (OH)
XIVa	3 450 – 3 320 (NH); 1 700 (C=O)	1.68 s, 3 H (CH_3); 7.12 s, 1 H (pyrazole CH); 7.30 – 7.41 m, 9 H (C_6H_5, C_6H_4); 8.70 – 8.75 2s, br, 3 H (3 × NH)
XIVb	3 450 – 3 320 (NH); 1 690 (C=O)	1.68 s, 3 H (CH_3); 7.04 s, 1 H (pyrazole CH); 7.33 – 7.38 m, 14 H (2 × C_6H_5, C_6H_4); 8.89, 9.74 2s, br, 2 H (2 × NH)

2,3-Diphenyl-6-(4'-methylphenylcarbamido)-5-thioxo-1,2,4-triazine (*XI*)

An ice cold solution of benzenediazonium chloride (0.01 mol) was added to a solution of *X* (3.1 g, 0.01 mol) in ethanol (50 ml) containing sodium acetate (10.0 g). The reaction mixture was left at 5 °C for 6 h with continueous stirring. The solid product so formed was collected by filtration.

2-Amino-4-benzoylamino-3-cyano-1-(4'-methylphenyl)pyridin-6-one *XII*

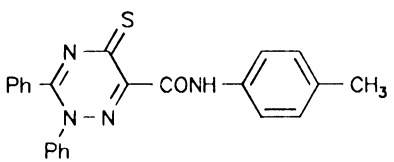
To a solution of *X* (3.1 g, 0.01 mol) in dioxane (30 ml) containing a catalytic amount of triethylamine (0.5 ml), malononitrile (0.66 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 6 h. The solid product formed upon pouring into ice/water containing few drops of hydrochloric acid was collected by filtration.

4-Benzoylamino-3-cyano-2-hydroxy-1-(4'-methylphenyl)pyridin-6-one (*XIII*)

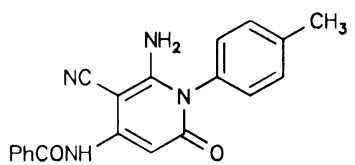
A mixture of equimolecular amounts of *X* (3.1 g, 0.01 mol) and ethyl cyanoacetate (1.13 g, 0.01 mol) containing a catalytic amount of piperidine (0.5 ml) was heated in an oil bath at 120 °C for 30 min. The solid product formed upon cooling was triturated with petroleum ether and collected by filtration.

3-Benzoylamino-5-(4'-methylphenylamino)pyrazole (*XIVa*) and 3-Benzoylamino-1-phenyl-5-(4'-methylphenylamino)pyrazole (*XIVb*); General Procedure

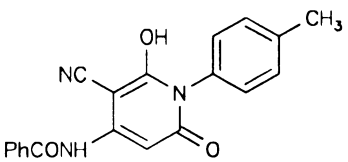
A mixture of *X* (3.1 g, 0.01 mol) and hydrazine hydrate (1 g, 0.02 mol) or phenyl hydrazine (3.6 g, 0.02 mol) was heated in a boiling water bath for 2 h, then was left to cool at room temperature. The solid product formed upon trituration with ethanol was collected by filtration.



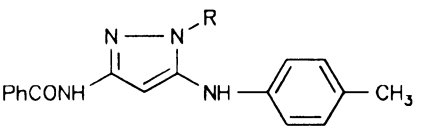
XI



XII



XIII



XIVa, R = H
XIVb, R = Ph

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