Reactions of 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one with Carboxylic Anhydrides: Experimental Data and AM1 Calculations

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1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one **1** reacts with several carboxylic anhydrides **2a-d** under different conditions and gives new amide and imide derivatives. The structure of these compounds, **3a-d,** are determined by spectroscopic methods. Electronic and geometric structures of reactants, transition states, intermediates and final products of the reaction are calculated by the AM1 method. Transition states are further confirmed by vibrational analysis (computation of force constants analytically) and characterized by the corresponding imaginary vibration modes and frequencies.

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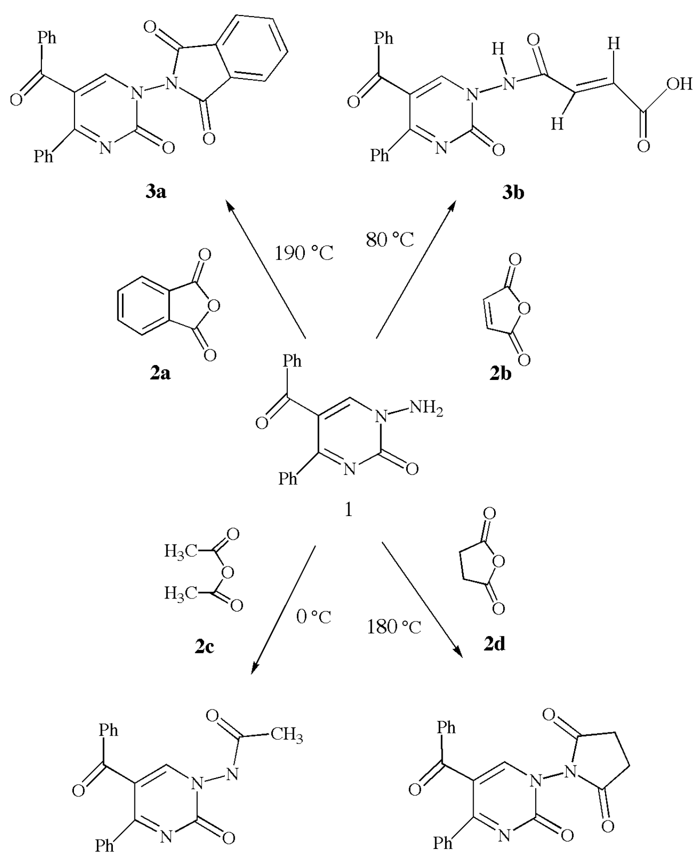
Introduction.

Pyrimidines in general have been found to be of much interest for biological and medicinal reasons, thus their chemistry has been extensively investigated [1,2]. Some of these compounds have been shown to exhibit bactericide, fungicide, antiviral and herbicide properties [3,4]. We have earlier reported that 4-benzoyl-5-phenylfuran-2,3-dione reacts with semicarbazones, ureas and their thio analogues forming 1*H*-pyrimidine derivatives [5,6,7,8]. Also conformational analysis and quantum chemical calculations were carried out by means of MMP2, CNDO, MNDO and AM1 approximation methods for the series of compounds being functionalised 1*H*-pyrimidines [9,10,11].

In this paper, the synthesis and characterization of pyrimidine derivatives **3a-d** obtained from the reaction between 1*H*-pyrimidine-2-one **1** and anhydrides **2a-d** are presented. To study the mechanism of the reaction all

Scheme 1



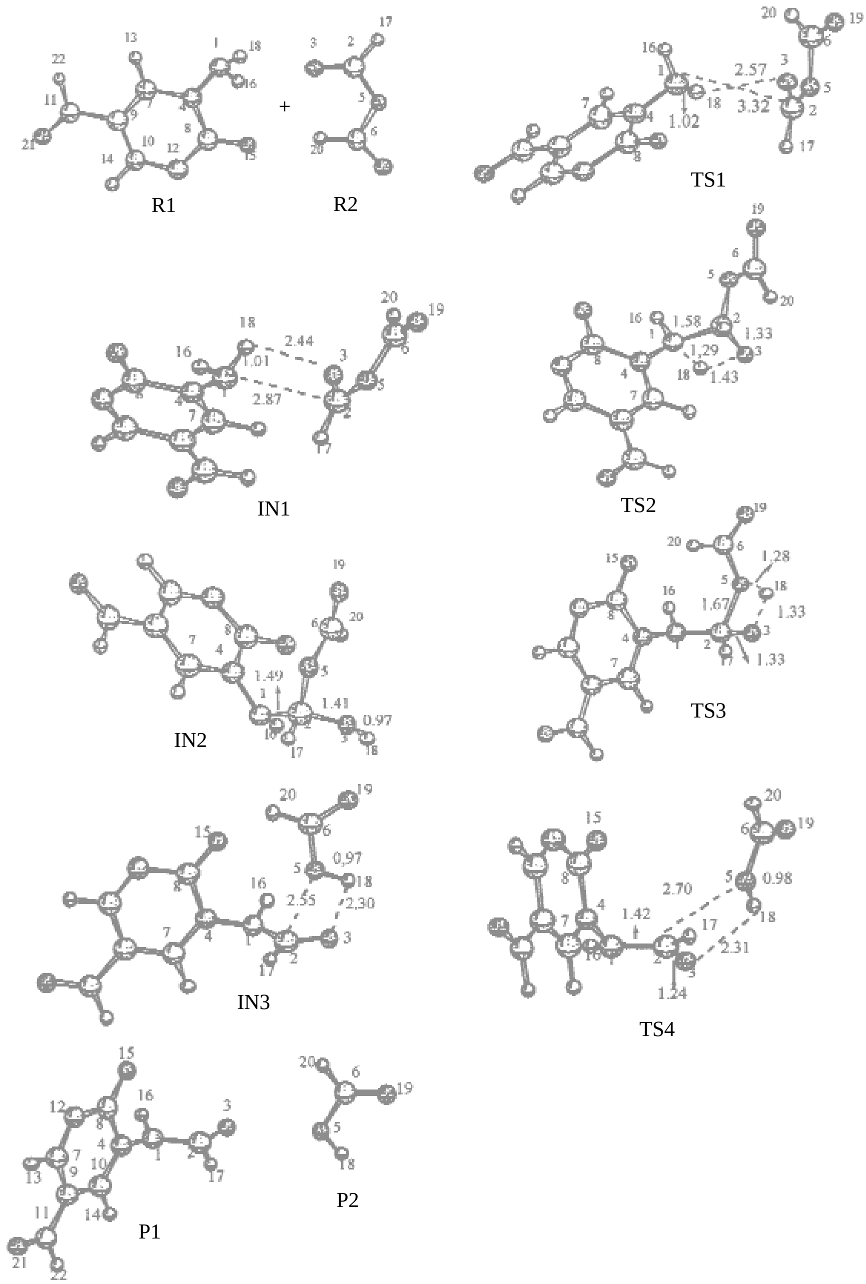
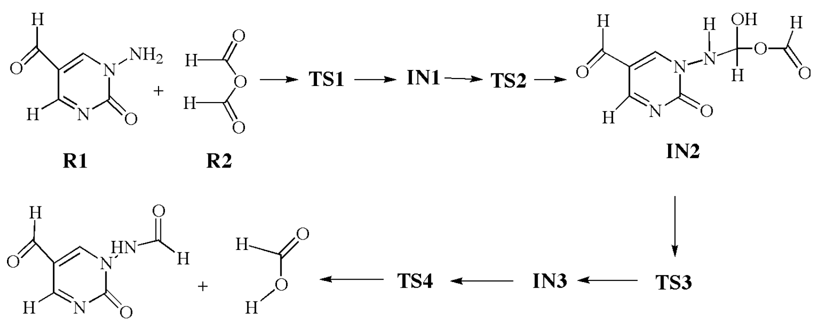


Figure 1. Atom-numbering scheme and structures of the reactants, transition states, intermediate and products (for structural date see table 3).

calculations were carried out by means of semiempirical AM1 methods [12] with full geometry optimization for reactants, products and intermediates. Transition structures, located with saddle calculations, were refined by minimizing the scalar gradient of energy with respect to the geometry and characterized as saddle points by diagonalising the Hessian Matrix (force constant) and establishing the presence of one and only one negative force constant, whereas the ground state of the reactants, the intermediate, and the products had no imaginary force constants. As a result, the transition states were located with the SADDLE routine in MOPAC and obtained structures were refined with TS option. The AM1 calculations were carried out with the help of the MOPAC 7 program package [13].

To clarify some steps of the reaction between 1*H*-amino-pyrimidine **R1** and anhydride **R2**, theoretical calculations were done for initials, transition states, intermediates and products of the reaction. To make calculations easier, the model compounds with alkyl, aryl and phenyl groups substituted by hydrogen atoms were used. The results of the calculations (energies, E_{rel} in kcalmol^{-1}, relative to the

Scheme 2



separated reactants 1*H*-amino-pyrimidine **R1 +** anhydride **R2**; dipole moments μ, in debye; the highest occupied molecular orbital energies E_{HOMO} and lowest unoccupied molecular orbital energies E_{LUMO} in eV and imaginary frequencies,$\bar{\nu}$ in icm^{-1}) are given in table 1.

Results and Discussion.

The reaction of the pyrimidine **1** with acid anhydride derivatives (see Scheme 1) **2a-d** yields *N*-acyl derivatives **3a-d**. The structures of **3a-d** are confirmed by their elemental analysis, ir, ^{1}H nmr and ^{13}C nmr spectroscopic data. Product **3a** with 55% yield is obtained by treating **1** with phthalic anhydride **2a** at 190 °C for 1 hour. The formation of **3a** is supported by the results of spectroscopic measurements, in particular showing the presence of three carbonyl bonds (ir: 1810, 1720, 1645 cm^{-1}; ^{13}C nmr: 187.8, 176.5, 165.4 ppm). Measurements results are given in the experimental section. The reaction of **1** with maleic anhydride **2b** at 80 °C for 1 hour gives **3b** with 53% yields. The structure of compound **3b** is easily determined from ir, ^{1}H and ^{13}C nmr spectra. The NH and OH absorption bonds are observed at approximately 3150 and at 2900-2700 cm^{-1} (broad), respectively; C=O absorption bands are also observed (ir: 1720, 1700, 1685, 1660 cm^{-1}; ^{13}C nmr 195.9, 168.5, 165.7 and 150.8 ppm). In the ^{1}H nmr spectrum, the peak corresponding to the –COOH is observed at δ = 11.32 ppm. Amide and alkenyl protons, –NH-CO–CH=CH-, are observed at δ = 5.43, 7.97 and 6.44 ppm, respectively. The same reaction was attempted at high temperatures (up to 200 °C), the pure imide derivatives like **3a** and **3d** were not obtained. When **1** is heated with succinic anhydride **2d** at 180 °C, **3d** is obtained in 60% yield. The results of measurements of **3c** and **3d** are given in the experimental. The important steps in the proposed mechanism for the reaction are presented in Scheme 2. The spatial dispositions of atoms for the reactants **R1-R2**, intermediates **IN1-IN3,** transition states **TS1-TS4** and the products **P1-P2** are shown in Figure 1. To simplify the study of changes in the systems, the same numbering of atoms is kept for the reactants, transition states, the intermediate and final products of reaction. According to Scheme 2, the interaction of the nucleophile (1*H*-primidine) with acid anhydride goes through several stages. Each stage of the reaction is characterized by electronic properties and

Table 1

Calculated (AM1) Relative Energies (E_{rel}, kcal.mol^{-1}), Dipole Moments, (μ, debye), HOMO Orbital Energies (E_{HOMO}, eV) and Imaginary Frequencies ($\bar{\nu}$, icm^{-1}) for the Reactants (**R1** and **R2**) Transition States (**TS1-TS4**), Intermediates (**IN1-IN3**) and Final Products (**P1** and **P2**)

Compounds	E_{rel} kcalmol^{-1}	μ Debye	E_{HOMO}, eV	E_{LUMO}, eV	$\bar{\nu}$,icm^{-1}
R1		4.32	-9.95	-0.97	
R2		2.07	-11.58	+0.08	
R1+R2	0.00				
TS1	5.3	6.50	-10.01	-1.17	-61.1
IN1	0.1	3.91	-9.88	-0.94	
TS2	56.3	4.77	-10.42	-1.59	-1930.0
IN2	2.2	6.03	-10.08	-1.16	
TS3	54.6	4.42	-10.31	-1.44	-1950.5
IN3	-1.6	5.16	-10.25	-1.35	
TS4	-0.6	4.82	-10.22	-1.29	-63.5
P1		1.89	-9.85	-0.98	
P2		1.48	-11.82	+0.96	
P1+P2	-1.4				

Table 2

Selected Structural Data for the Reactants, Transition States, Intermediates and Final Products

Bond Lengths	**R1+R2**	**Ts1**	**In1**	**TS2**	**In2**	**Ts3**	**In3**	**Ts4**	**P1+P2**
C2-N1	4.11	3.32	2.87	1.58	1.49	1.44	1.42	1.42	1.42
O3-C2	1.23	1.23	1.23	1.33	1.41	1.33	1.24	1.24	1.24
N4-N1	1.37	1.37	1.37	1.38	1.37	1.37	1.36	1.36	1.36
O5-C2	1.36	1.37	1.37	1.41	1.42	1.67	2.55	2.70	4.14
C6-O5	1.40	1.39	1.39	1.38	1.39	1.36	1.36	1.36	1.36
H16-N1	1.02	1.01	1.02	1.02	1.02	1.01	1.01	1.01	1.01
H17-C2	1.11	1.11	1.11	1.12	1.13	1.12	1.11	1.11	1.11
H18-03	2.45	2.57	2.44	1.43	0.97	1.33	2.30	2.31	4.35
H18-N1	1.02	1.01	1.01	1.29	3.15	2.98	3.72	3.99	3.13
H18-O5	4.41	4.23	3.98	2.88	2.55	1.28	0.97	0.98	1.07
Bond Angles									
O3-C2-N1	2	63	79	92	109	115	119	118	119
N4-N1-C2	127	128	121	120	118	119	121	121	121
O5-C2-O3	120	119	117	110	105	86	74	140	78
C6-O5-C2	121	120	121	119	118	137	145	150	129
C7-N4-N1	118	123	119	119	118	118	119	119	119
C8-N4-N1	123	119	122	122	123	123	122	122	122
H16-N1-C2	52	118	130	112	107	113	116	116	125
H17-C2-O3	129	130	79	113	114	119	125	117	89
H18-O3-C2	158	108	88	86	108	92	99	80	118
H20-C6-O5	118	117	118	118	118	117	112	112	123
Torsion Angles									
N4-N1-C2-O3	41	144	57	118	-121	173	-165	-163	-162
O5-C2-O3-N1	131	-109	118	116	-128	-116	-103	101	-159
C6-O5-C2-O3	0	13	-96	-93	50	136	117	-13	62
C7-N4-N1-C2	-173	-138	5	-55	-92	-89	-96	-103	-97
C8-N4-N1-C2	9	42	180	125	95	99	87	78	86
H16-N1-C2-O3	-44	-60	-139	-114	0.71	-54	-23	-21	-21
H17-C2-O3-N1	-49	73	-136	-125	118	144	175	-176	175
H18-O3-C2-N1	-46	-15	15	1	-153	115	110	-128	171
O19-C6-O5-C2	180	-170	177	176	-177	-144	-133	-110	-134

energy states. With N1-C2 bond length of 4.11Å (see Table 2), there is no interaction between **R1** and **R2**, in this case the formation energy for **R1+ R2** is equal to the sum of the formation energies of reactants, **R1** and **R2**. When the N1-C2 bond length becomes 3.32 Å, interaction occurring between reactants, **R1** and **R2**, leads to first transition state **TS1**. At the transition state **TS1** (E_{rel} = 5.3 kcalmol^{-1}), molecular planes of the **R1** and **R2** molecules approach at an angle of 144° and the N4-N1-C2-O3 atoms are not coplanar. At the **IN1**, N4-N1-C2-O3 torsion angle and the N1-C2 bond length are 57° and 2.87 Å, respectively (see Table 2). The low level of the relative energy of **TS1** can be explained by the fact that **TS1** is very similar in structure to **R1+R2** and very low values are found for rotational motions but not for formation of chemical bonds (see Table 2). As given in Table 3, the zero bond order between atoms C2 and N1 in the species **R1+R2**, **TS1** and **IN1** indicates that there is no bond formation for C2-N1. The second transition structure, **TS2** (see Figure 2) corresponds to the nucleophlic addition of the amino group on pyrimidine to the sp^2 hybridized carbon atom of the electrophilic anhydride to give the **IN2**. The reacting atoms approach cause the N1-H18 bond length to increase and C2=O3 double bond to weaken. As seen from the data in Table 2, the formation of N1-C2 and O3-H18 bonds leads simultaneously to the weakening of N1-H18 bond. The transition state **TS2** (E_{rel} = 56.3 kcalmol^{-1}) is characterized by the presence of a four membered cycle with the bond lengths substantially changed as compared with their **IN2** values. For **TS2**, the bond distances N1-C2, C2-O3, O3-H18 and N1-H18 are 1.58, 1.33, 1.43 and 1.29 Å, respectively. Further approach of the atoms N1 and C2 finally leads to the formation of N1-C2 and O3-H18 bonds and breaking of N1-H18 bond.

As shown in Table 2, the reaction results in the rearrangements of bonds and valence angles in the reacting systems. The value of valence angle of N1-C2-O3 at the

Table 3

Mulliken Charge and Bond Order Selected Atoms for the Reactants, Transition States, Intermediates and Final Products

Atoms charge	**R1+R2**	**Ts1**	**In1**	**Ts2**	**In2**	**Ts3**	**In3**	**Ts4**	**P1+P2**
N1	-0.18	-0.19	-0.20	-0.17	-0.17	-0.23	-0.27	-0.27	-0.27
C2	0.30	0.30	0.30	0.25	0.20	0.31	0.28	0.27	0.25
O3	-0.38	-0.37	-0.37	-0.53	-0.36	-0.42	-0.32	-0.32	-0.30
N4	-0.22	-0.23	-0.22	-0.25	-0.22	-0.21	-0.19	-0.19	-0,20
O5	-0.18	-0.30	-0.31	-0.32	-0.32	-0.45	-0.36	-0.36	-0.33
C6	0.26	0.27	-0.26	0.26	0.25	0.27	0.26	0.27	0.26
O19	-0.26	-0.27	-0.26	-0.29	-0.28	-0.32	-0.36	-0.35	-0.36
H16	0.17	0.16	0.19	0.22	0.21	0.23	0.24	0.24	0.24
H18	0.18	0.17	0.15	0.33	0.24	0.38	0.25	0.26	0.24
Bond order									
C2-N1	0.00	0.00	0.00	0.72	0.93	0.96	0.98	0.99	0.98
O3-C2	1.82	1.84	1.83	1.21	0.99	1.29	1.86	1.85	1.87
N4-N1	0.96	0.97	0.96	0.94	0.96	0.95	0.95	0.95	0.95
O5-C2	1.02	1.00	1.01	0.93	0.99	0.52	0.01	0.00	0.00
C6-O5	0.89	0.93	0.92	0.96	0.95	0.97	1.05	1.05	1.06
H16-N1	0.95	0.95	0.94	0.91	0.92	0.90	0.89	0.89	0.89
H18-03	0.00	0.00	0.00	0.37	0.92	0.42	0.00	0.00	0.00
H18-N1	0.95	0.94	0.95	0.50	0.02	0.02	0.00	0.00	0.00
H18-O5	0.00	0.00	0.00	0.00	0.00	0.41	0.90	0.90	0.91

IN2 is close to that of bonds in sp^3 hybridized carbon (109°). The torsion angle of N1-C2-O3-H18, -153° clearly shows that the atoms are not coplanar. As seen from the data in table 2, the occurrence of **IN3** in the reaction pathway involves a 1,2-shift of the H18 atom to the O5 atom *via* a four centered transition state **TS3** in where partial formation of the O5-H18 bond and partial breaking of the O3-H18 bond take place simultaneously. The **TS3**, like **TS2**, has a four-center structure involving C2,O3,O5 and H18 atoms and these four atoms are nearly coplanar with dihedral angle of 1°. The H18-03 bond length in **TS3**, **IN3**, **TS4** and **P1+P2** becomes 1.33, 2.30, 2.31 and 4.35 Å, respectively. The other bond lengths, bond angles and torsion angle are given in Table 2. Further separation of the formic acid molecule **P2** from the amide derivative **P1** returns the C2 atom to the sp^2 hybridization state. Concurrent with sp^2 hybridization of C2, double bond formation between C2 & O3 takes place along with proton migration from the O3 atom to the O5 atom. The low level of the relative energy of **TS4** can be accounted for on the grounds that it is similar in structure to the products **P1+P2** as explained above for **TS1**, such low values are found for rotational motions (see Table 2).

The reactivity of the acid anhydride depends upon their ability to accept the reactant 1*H*-pyrimidine molecule. The ability of the nucleophilic 1*H*-primidine molecule to add to a carbonyl group depends not only on the charge of the carbonyl carbon atom but also the charge separation between carbon and oxygen of the carbonyl group. Charge separation for the N1, C2, O3 and H18 atoms of all structures are given in the table 3. Bond orders were calculated as the sum of the squares of density matrix elements connecting two atoms by the bonds routine implemented in MOPAC7 [13]. Bond orders can be used as a measure of the degree of advancement of the transition state along a reaction path [14,15]. Table 3 shows the bond orders throughout the reaction paths of the model reactions used in this study. As going from **R1+R2** to **IN2** during the reaction, N1-H18 and C2-O3 bond strengths decrease and N1-C2 bond strength increases. Also for the case **IN2** to **P1**+**P2**, O5-C2 bond strength decreases and O5-H18 bond degree increases.

EXPERIMENTAL

Solvents were dried by refluxing with the appropriate drying agent and distilled before use. Melting points were determined by use of a Büchi melting point apparatus and not corrected. Microanalyses were performed on a Carlo Erba Elemental Analyzer Model 1108. The ir spectra were obtained in as potassium bromide pellet using a Shimadzu Model 435 V-04 spectrometer. The ^{1}H and ^{13}C nmr spectra were recorded on a Varian 4200 Gemini spectrometer using tetramethysilane as an internal standard. All experiments were followed by TLC using DC Alufolion kieselgel 60 GF 254 Merck and with a Model Camag TLC lamp (254/366 nm).

2-(5-Benzoyl -2-oxo-4-phenyl-1,2-dihydro-1-pyrimidinyl)-1,3-isoindolinedione (**3a**).

1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one **1** (0.2 g) and a large excess of phthalic anhydride **2a**, 1.6 g, (molar ratio 1:32) were homogeneously mixed. The mixture was heated at 190 °C for 1 hour without any solvent in a 50 ml round bottomed flask equipped with a calcium chloride guard tube. After cooling to room temperature the residue was treated with dry ether and the crude product recrystallized from 1-butanol, yield 0.16 g (55%); mp 326 °C; ir (potassium bromide): ν 3450 (C=O, carbonyl overtone), 3020 (aromatic C-CH), 1810-1720-1645 (C=O carbonyl), 1500-1460 (aromatic ring. Skeleton vib), 1300-1050 (anhydride C-O stretch.), 800-700 (pyrimidine ring) cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.10-8.03 (m, 15H, aromatic), 8.99 (s, 1H, pyrimidine ring), 3.34 (s, 2H, under the peak of H_2O in DMSO probably); ^{13}C nmr (DMSO-d_6): δ 187.81 (s, benzoyl's C=O), 165.40 (s, isoindoline's C=O), 154.49 (s, primidine's C=O) 176.46-119.30 (m, aromatic C).

Anal. Calcd. for $C_{25}H_{15}N_3O_4$: C, 71.25; H, 3.42; N, 10.07. Found: C, 71.28; H, 3.42; N, 10.07.

3-(5-Benzoyl-2-oxo-4-phenyl-2*H*-pyrimidin-1-ylcarbamoyl)-2-propenoic Acid (**3b**).

1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one **1** (0.2 g) and 0.8 g maleic anhydride **2b** (molar ratio1:13) were homogeneously mixtured. The mixture was heated at 80 °C for 1 hour without any solvent in a 50 ml round bottomed flask equipped with a calcium chloride guard tube. After cooling to room temperature the residue was treated with dry ether and then the precipitated crude white product was isolated by filtration. The crude product washed from benzene. 0.07 g (53%); mp 148 °C; ir (potassium bromide): ν 3150 (N-H), 2900-2700 (broad, acid's O-H), 1720,1700,1685,1660 (C=O absorption bend), 1520-1400 (aromatic ring. Skeleton vib.), 780-680 (pyrimidine ring) cm^{-1}; ^1H nmr (DMSO-d_6): δ 11.32 (s, -COOH), 6.44, 7.97 (m, -CH=CH-COOH respectively), 5.43 (broad, NH), 8.50 (s, 1H, pyrimidine ring), 8.05-6.78 (m,10H, aromatic) ppm; ^{13}C nmr (DMSO-d_6): δ 195.84(s, benzoyls C=O), 168.50 (s, carboxyl's C=O), 165.7 (s, amide's C=O), 150.76 (s, pyrimidine's C=O), 128.7 and 127.3 (propenyl's C), 178.5-119.3 (m, aromatic C) ppm.

Anal.Calcd.for $C_{21}H_{15}N_3O$: C, 64.78; H, 3.85; N,10.79 Found C, 64.10; H, 3.70; N, 10.37

N-(5-Benzoyl-2-oxo-4-phenyl-1,2-dihydro-1-pyrimidinyl) Acetamide (**3c**)

1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one **1** (0.2 g) and 2 ml acetic anhydride **2c** (molar ratio 1:33) were mixed at 0 °C for 3-4 hours. The residual acetic anhydride was removed by evaporation and the oily residue was treated with anhydrous ether to give a white colored crude solid which was recrystallized from 1-butanol yielding 0.15 g (68 %), mp 328 °C; ir (potassium bromide): ν 3200 (N-H), 3020 (-CH_3), 1730-1660 (C=O groups), 1610-1590 (C=C and C=N), 1500-1450 (arom. skeleton. vib.), 800-670 (pyrimidine ring. Skeleton .vib) cm^{-1}. ^1H nmr (DMSO-d_6): δ 8.70 (s, 1H, pyrimidine ring), 6.52 (Broad, NH), 8.12-7.75 (m, aromatic 10H), 2.11 (s, CH_3).

Anal.Calcd. for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.50; N, 12.61 Found: C, 68.51; H,4.68; N,12.37.

N-(5-Benzoyl-phenyl-2-thioxo-1,2-dihydro-1-pyrimidinyl)-2,5-pyrrolidine dione (**3d**).

1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one **1** (0.2 g) and 1.5 g succinic anhydride **2d** (1:22 molar ratio) were heated at 180 °C for at 4 hours without any solvent. The residue was then treated with dry ether and the crude product isolated filtration. The crude product so formed was recrystallized from 1-butanol. 0.15 g (60%), mp 321 °C ; ^1H nmr (DMSO-d_6): δ 8.67 (s, 1H, pyrimidine ring), 2.52 (s, CH_2), 8.16-7.49 (m, aromatic 10H) ppm.

Anal. Calcd. for $C_{21}H_{15}N_3O_4$: C, 67.56; H, 4.04; N, 11.25 Found: C, 67.20; H, 3.90; N, 11.20.

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