Studies on the Reactions of Cyclic Oxalyl Compounds With Hydrazines or Hydrazones : Synthesis and Reactions of 4-Benzoyl-1-(3-Nitrophenyl)-5-Phenyl-1*H*-Pyrazole-3-Carboxylic Acid

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The 1*H*-pyrazole-3-carboxylic acid **2**, obtained from the furan-2,3-dione **1** and *N*-Benzylidene-*N'*-(3-nitrophenyl) hydrazine, was converted *via* reactions of its acid chloride **3** with various alcohols or N-nucleophiles into the corresponding ester or amide derivatives **4** or **5**, respectively. Nitrile **6** and anilino-pyrazole acid **7** derivatives of **2** were also obtained by dehydration of **5a** in a mixture of $SOCl_2$ with DMF and reduction of **2** with sodium polysulphide, respectively. While cyclocondensation reactions of **2** or **7** with phenyl hydrazine or hydrazine hydrate and **6** with only anhydrous hydrazine lead to derivatives of pyrazolo[3,4-*d*]-pyridazinone **8** and pyrazolo[3,4-*d*]pyridazine amine **9**, respectivel. The reaction of **2** with 2-hydrazinopyridine provided hydrazono-pyrazole acid derivative **10**, which was decarboxylated to give hydrazono-pyrazole derivative **11**. Pyrazolo[4,3-*d*]oxazinone **12** and 2-quinolyl pyrazolo[3,4-*d*]pyridazine **13** derivatives were also prepared by cyclocondensation reactions of **2** with hydroxylamine hydrochloride and **7** with acetaldehyde, respectively.

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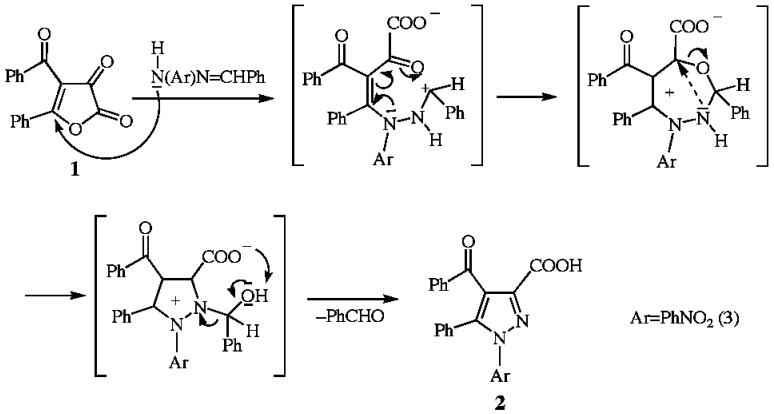
Pyrazole chemistry has been the focus of high attention for more than three decades due to versatile biological activities of pyrazole derivatives appearing as anti-microbial [1], anti-viral [2], anti-tumor [3], anti-inflammatory [4], anti-histaminic [5] pesticidal [6], anti-fungal [7], against rheumatoid arthritis [8], anti-convulsant [9], anti-depressant [10] and anti-pyretic [11] agents. Our studies related to preparing pyrazole and fused pyrazole derivatives by the functionalization and cyclization reactions of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid with various nucleophiles was previously reported [12,13]. In this last study, we attempted both to prove reproducibility of the reaction of furandione **1** with another hydrazone and to extend our investigations related to preparing new pyrazole derivatives.

In this work, we studied the reaction of furandione **1** with *N*-benzylidene-*N'*-(3-nitrophenyl) hydrazine. Without any solvent, heating of furandione **1** and hydrazone (1/1 mole) neat about 1 hour, the time during which benzaldehyde odor is detected, led to the formation of the titled compound 2 in approximately 55% yield. The moderate yield of the reaction can be explained by the chemical behavior of furandione **1** towards H-active nucleophiles. Addition of nucleophiles to furandione **1** usually starts with nucleophilic attack at one of the C-2, C-3 and C-5 positions of the furan ring system. Simultaneous attack of H-active nucleophiles to both C-2 and C-3 positions of furan ring could convert furandione **1** into starting materials; these materials are dibenzoylmethane and oxalic acid derivatives [14]. The by-products formed this way, are removed when the raw product is treated with ether or toluene.

A reasonable proposal different from that discussed with phenyl hydrazone [13] for reaction pathway from furandione **1** to pyrazole carboxylic acid **2** is outlined briefly in Scheme 1.

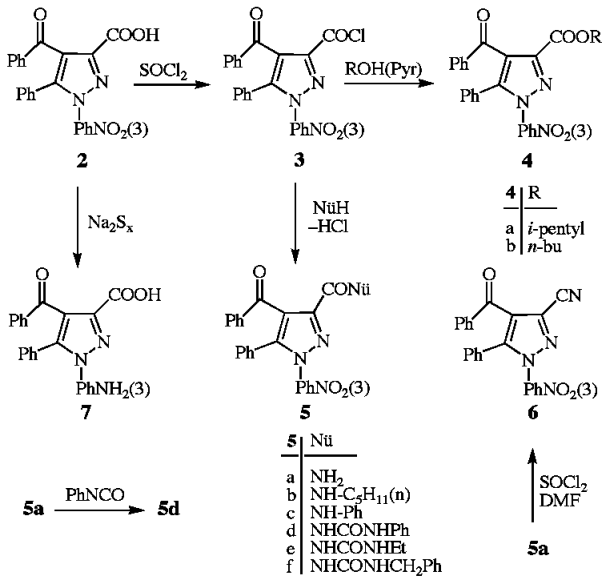
Scheme 1



Ring opening for the formation of first intermediate may be initiated by nucleophilic attack of the NH group adjacent to the phenyl ring of hydrazone at the C-5 position of the furandione ring similar to the reactions of furandione **1** with various H-active nucleophiles [15]. Ring closure of the first intermediate to the oxadiazepine intermediate *via* addition of N=CHPh group to the C=O moiety takes place by the catalytic effect of carboxylic acid proton similar to the addition of azines to furandiones [16]. Rearrangement of the second intermediate generates the pyrazole carboxylate intermediate, and finally loss of benzaldehyde gives compound **2**.

Structure of compound **2** was confirmed by analytical and spectral data. In addition, the acid **2** could be easily converted into the corresponding acid chloride **3**, ester **4**, amide **5** and nitrile **6** derivatives by conventional chemical procedures (Scheme 2). The pyrazole-3-carboxylic acid chloride **3**, obtained in approximately 65% yield, is remarkably stable.

Scheme 2

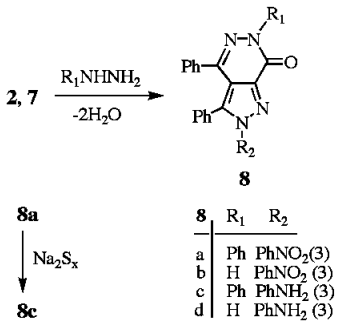


The correct structures of the unsymmetrically substituted urea derivatives **5d-f** were established by another chemical procedure consisting of the reaction of the primary amide **5a** with phenylisocyanate which resulted in formation of phenylurea derivative **5d**, originally prepared from the acid chloride **3** in the usual way.

Reduction of **2** with sodium polysulphide led to form the derivative of anilino-pyrazole acid **7** (Scheme 1). Structure of the anilino acid **7** was proved by analytical and spectral data (See experimental). In addition, cyclization derivatives of the anilino-pyrazole acid with hydrazines **8c,d** and acetaldehyde cyclize to give quinoline derivatives, structures of which were also elucidated by elemental analysis and spectroscopic data (Scheme 7).

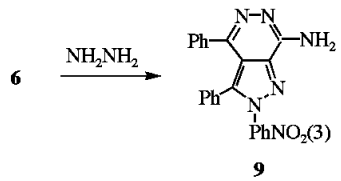
Reactions of pyrazole derivative having the dicarbonyl groups in the suitable position with hydrazines are convenient methods to build the pyrazolo[3,4-*d*]pyridazine systems [12,17]. Thus, the pyrazole acids **2**,**7** were cyclized with hydrazines to the pyrazolo[3,4-*d*]pyridazinones **8a-d**, in approximately 45-66 % yields. Additionally, **8c** was also obtained by the second method which is reduction of **8a** with sodium polysulphide (Scheme 3).

Scheme 3



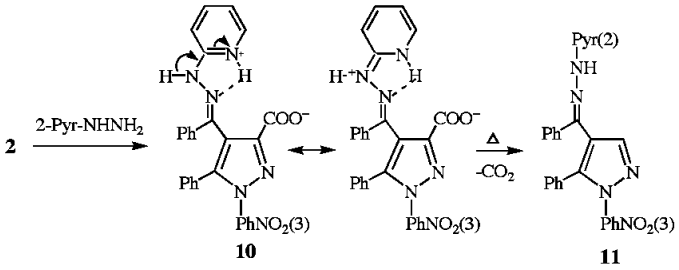
In a similar way, pyrazole-3-carbonitrile **6** with anhydrous hydrazine in boiling 1-butanol containing a catalytic amount metallic sodium was also cyclized to the 7-aminopyrazolo[3,4-*d*]pyridazine derivative **9** in approximately 35% yield (Scheme 4). Structure elucidation of **8a-d** and **9** is mainly based on ^{13}C-nmr spectroscopy (See experimental for details).

Scheme 4



On the other hand, the reaction of **2** with 2-hydrazinopyridine instead of phenylhydrazine or hydrazine hydrate did not lead to form the corresponding pyrazolo-pyridazine derivative. Surprisingly, however, 2-hydrazinopyridine was added to **2** to yield a new pyrazole acid **10** containing a hydrazone group; hydrazono-pyrazole acid of this type from analogous pyrazole acids have not been described previously [12,13]. The failure or the difficulty in forming the pyridazine nucleus from **10** can be explained by low nucleophilicity of the nitrogen atom adjacent to the pyridine ring. Additionally, decarboxylation of **10** on an oil-bath at elevated temperature led to cleavage of C-C bond with loss of CO_2 finally yielding the corresponding hydrazono-pyrazole derivative **11** (Scheme 5).

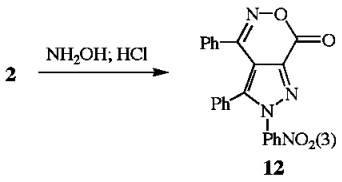
Scheme 5



Compound **10** and **11** show characteristic ir absorption bands at 3437 cm^{-1} (NH), 1651 cm^{-1} (C=N), 3361 cm^{-1} (NH) and 1676 cm^{-1} (C=N). Ir spectra of compound **10** showed no absorption bands corresponding to the COOH group such as 3300-2500 cm^{-1} (b, OH, COOH) and 1700-1750 cm^{-1} (C=O, COOH) like that of 4-benzoyl-1,5-diphenyl pyrazole-3-carboxylic acid [13]. However, absorbtion bands at approximately both 1610 cm^{-1} and 1577 cm^{-1} corresponding to ionized carboxylate group [18] were observed. From its ir spectrum, it may be deduced that the compound **10** is found as the betaine form in the solid state. Their characteristic ^{1}H- nmr signals at δ =10.2 (b, 1H, acidic proton), 8.92 (b, 1H,NH), 8.25-6.57 ppm (m, 18H, ArH) and 8.70 (b, 1H, NH), 8.48-6.84 ppm (m, 19H, ArH) and ^{13}C-nmr signals at δ =167.06 (COO), 157.9 (C-2', Pyr), 146.13 ppm (C=N) and 156.83 (C-2', Pyr), 154.73 ppm (C=N), respectively, are in full agreement with their proposed structures.

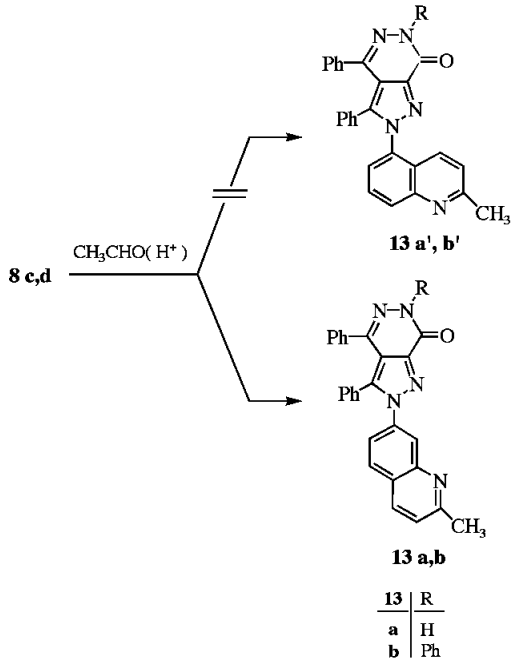
Additionaly, direct reaction of **2** with hydroxylamine hydrochloride, on an oil-bath at approximately 150-155 °C led to the formation of the pyrazolo[4,3-*d*]oxazinone **12** in about 65% yield (Scheme 6). The structural proof of **12** is based on elemental analysis and spectral data (See experimental).

Scheme 6



Finally, cyclization reactions of compounds **8c-d** with acetaldehyde in strong acidic medium lead to form quinoline derivatives **13a-b**. Thus, the stability of the compounds of type **8** in strong acidic medium was also confirmed by these reactions, outlined briefly in Scheme 7. Due to lack of substituents at the *ortho*- positions relative to the amino group, the Skraup reaction of anilino-pyrazolo-pyridazinones **8c-d** may produce two isomeric quinoline derivatives [19]. However, the results of tlc studies for each reaction illustrate the presence of only one product, the probable structure of which was identified as 2-(2-methylquinolin-7-yl)-pyrazolo[3,4-*d*]pyridazin-7-one derivatives **13a** or **13b**. The choice of one of the two alternative structures is based on the ^{1}H-nmr spectra of **13a** and **13b**, where a few signals are observed down-field in the aromatic region compared to the ^{1}H-nmr signals of **8 c** and **8 d**.

Scheme 7



The probable structures of compounds **13 a,b** are supported by elemental analysis and spectroscopic data. In the ir spectra of **13a** and **13b**, characteristic absorption bands at about 3455 cm^{-1} (NH⇆OH), 1673 cm^{-1} (C=O) and 1676 cm^{-1} (C=O) were observed, respectively. In the ^{1}H-nmr spectra of compounds **13** the signals corresponding to NH_2 groups observed in compounds **8c,d** are not present, and with the exception of singlet signal for methyl groups at δ =2.64-2.69, all signals appeared in the aromatic region. Also, the ^{1}H-nmr spectra of **13a** and **13b** show that H-4' and H-6' appear as a doublet at δ =8.30 (J=8.4 Hz)-8.05 (J=8.4 Hz) and δ =8.00 (J=8.8 Hz)-7.98 (J=9.2 Hz), respectively. Also, signals corresponding to H-8' at δ =7.91(J < 2 Hz)-7.88 (J < 2 Hz) were observed as a multiplet; the very slight splitting indicates the absence of a vicinal proton next to H-8'. This evidence establishes the reaction route **8 c,d → 13 a,b**, and rules out the formation of compounds **13 a',b'**. Other spectral and analytical data of **13 a** and **13 b** are in full agreement with their proposed structures as well(see experimental).

EXPERIMENTAL

Solvents were dried by refluxing with the appropriate drying agents and distilled before use. Melting points were determined

on an Electrothermal Gallenkamp apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyser Model 1108. The ir spectra were obtained as potassium bromide pellets using a Mattson 1000 FTIR spectrometer. The ^{1}H and ^{13}C-nmr spectra were recorded on ASR 18 YUICH (200 MHz) and ASR 18 YUICH (50 MHz) spectrometers, respectively, using TMS as an internal standard. The mass spectrum of **2** was measured on a Varian mat III at 80 eV. All experiments were followed by tlc using DC Alufolien Kieselgel 60 F 254 Merck and Camag TLC lamp (254/366 nm).

4-Benzoyl-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic Acid (**2**).

An equimolar mixture of furandione **1** (0.278 g, 1 mmole) and (3-nitrophenyl hydrazono) (phenyl) methane (0.241 g, 1 mmole) was heated to 85-90 °C for approximately 60 minutes, at which time the odor of the benzaldehyde was no longer detectable, without any solvent. After cooling to room temperature, the residue was treated with dry toluene and the formed crude product was recrystallized from ethanol to give 0.227 g (55%) of a colorless solid, mp 210 °C (decomp.); ir: 3400-2500 cm^{-1} (b, OH, COOH), 1716 cm^{-1} (C=O, COOH), 1670 cm^{-1} (C=O, benzoyl); ^{1}H-nmr (deuteriochloroform): δ 8.28 (s, H-2'), 7.82-7.21 ppm (m, ArH); ^{13}C-nmr (deuteriochloroform): δ 193.53 (C=O, benzoyl), 165.41 (C=O, COOH), 150.35 (C-NO_2), 147.10 (C-3), 144.43 (C-5), 141.47 (N-PhNO_2), 139.25 (C-Ph), 135.53, 132.91, 132.07, 132.02, 131.88, 131.45, 130.98, 130.37, 128.91 (C-Ph), 125.53 (C-4), 125.33, 122.51 ppm. Mass (80 eV): m/e= 414.1; 385.3; 369.3; 352.8.

Anal. Calcd. for $C_{23}H_{15}N_3O_5$: C, 66.83; H, 3.66; N, 10.16. Found: C, 66.69; H, 3.67, N, 10.18.

4-Benzoyl-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl Chloride (**3**).

Compound **2** (0.413 g, 1 mmole) and thionylchloride (1 ml., 13.8 mmoles) were refluxed on a steam bath for 5 hours. After cooling, the crude precipitate was isolated by filtration and recrystallized from a mixture of toluene and *n*-hexane, yield 0.281 g (65%), mp 166 °C; ir: 1758 cm^{-1} (C=O, acyl), 1676 cm^{-1} (C=O, benzoyl); ^{13}C-nmr (deuteriochloroform): δ 191.55 (C=O, benzoyl), 163.61 (C=O, acyl), 150.48 (C-NO_2), 147.09 (C-3), 146.93 (C-5), 141.34 (N-PhNO_2), 138.96 (C-Ph), 135.99, 132.81, 132.40, 132.28, 131.69, 131.39, 131.17, 130.72, 128.40 (C-Ph), 126.14 (C-4), 125.68, 122.48 ppm.

Anal. Calcd. for $C_{23}H_{14}N_3O_4Cl$: C, 63.97; H, 3.27; N, 9.73; Cl, 8.21. Found: C, 63.92; H, 3.26, N, 9.71; Cl, 8.19.

Isopentyl 4-Benzoyl-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (**4a**).

General Procedure.

The acid chloride **3** (0.431 g, 1 mmole) and a moderate excess of the isopentyl alcohol were refluxed together with a catalytic amount of pyridine for 3 hours. After cooling, the solution was acidified by adding diluted hydrochloric acid (12%) to give a crude solid that was recrystallized from the same alcohol. The yield 0.387 g (80%), mp 160 °C (isopentyl alcohol); ir: 1753 cm^{-1} (C=O, ester), 1676 cm^{-1} (C=O, benzoyl); ^{13}C-nmr (deuteriochloroform): δ 192.47 (C=O, benzoyl), 162.98 (C=O,ester), 150.38 (C-NO_2), 145.84 (C-3), 145.36 (C-5), 141.74 (N-PhNO_2), 139.83 (C-Ph), 135.48, 132.81, 131.97, 131.91, 131.77, 131.40, 130.99, 130.67, 129.13 (C-Ph), 125.73 (C-4), 125.06, 122.46, 66.28 (O-CH_2), 38.80 (CH), 26.66 (CH_2), 24.27 ppm (CH_3).

Anal. Calcd. for $C_{28}H_{25}N_3O_5$: C, 69.55; H, 5.21; N, 8.69. Found : C, 69.61; H, 5.24; N, 8.66.

Butyl 4-Benzoyl-1-(3-nitrophenyl)-5-phenyl-*1H*-pyrazole-3-carboxylate (**4b**).

Compound **4b** was obtained in 82% yield (0.385 g); mp 175°C (n. butanol); ir: 1753 cm^{-1} (C=O, ester), 1676 cm^{-1} (C=O, benzoyl).

Anal. Calcd. for $C_{27}H_{23}N_3O_5$: C, 69.07; H, 4.94; N, 8.95. Found : C, 68.87; H, 4.95; N, 8.93.

4–Benzoyl-1-(3-nitrophenyl)-5-phenyl-1*H*–pyrazole-3-carboxamide (**5a**).

A moderate stream of gaseous ammonia was allowed to bubble through a solution of pyrazole-3-carboxylic acid chloride **3** (0.432 g, 1 mmole) in 20 ml of carbon tetrachloride during 30 minutes with ice-cooling. Then the crude precipitate was isolated by filtration and recrystallized from methanol to give 0.268 g (65%) of **5a**, mp 210 °C, ir: 3489 cm^{-1} (NH_2), 1676 cm^{-1} (C=O, benzoyl), 1638 cm^{-1} (C=O, amide). ^{1}H-nmr (DMSO-d_6): δ 5.74 and 7.0 (b, NH_2), 7.15-8.33 ppm (m, 14H, ArH).

Anal. Calcd. for $C_{23}H_{16}N_4O_4$: C, 66.99; H, 3.91; N, 13.59. Found: C, 67.23; H, 3.90, N, 13.65.

4-Benzoyl-1-(3-nitrophenyl)-*N*-pentyl-5-phenyl-1*H*-pyrazole-3-carboxamide (**5b**).

General Procedure.

An equimolar mixture of the acid chloride **3** (0.431 g, 1 mmole) and *n*-pentyl amine (1 mmole) was refluxed in xylene for 3 hours. After evaporation, the oily residue was treated with dry ether and the formed crude product was recrystallized from isopropanol. The yield 0.29 g (60%), mp 179 °C; ir : 3361 cm^{-1} (NH), 1676 cm^{-1} (C=O), 1642 cm^{-1} (C=O, amide); ^{1}H-nmr (deuteriochloroform): δ 7.11-8.31 (m, 14H, ArH), 3.34 (t, 2H, N-CH_2), 1.54 (m, 2H, CH_2), 1.28 (m, 2H, CH_2), 1.15 (m, 2H, CH_2), 0.85 ppm (t, 3H, CH_3); ^{13}C-nmr (deuteriochloroform): δ 193.37 (C=O), 162.09 (C=O), 150.43 (C-NO_2), 148.57 (C-3), 145.80 (C-5), 141.84 (N-PhNO_2), 139.90 (C-Ph), 135.20, 132.50, 131.97, 131.82, 131.71, 131.37, 130.94, 130.33, 129.43 (C-Ph), 127.77, 122.10 (C-4), 41.33 (N-CH_2), 31.28 (CH_2), 31.04 (CH_2), 24.32 (CH_2), 15.96 ppm (CH_3).

Anal. Calcd. for $C_{28}H_{26}N_4O_4$: C, 69.70; H, 5.43; N, 11.61; found : C, 69.82; H, 5.39, N, 11.58.

4-Benzoyl-1-(3-nitrophenyl)-*N*-phenyl-5-phenyl-1*H*-pyrazole-3-carboxamide (**5c**).

Compound **5c** was prepared by the general procedure above with a reflux time of 1 hour (aniline) resulting in a yield of 55% (0.269 g); mp 203 °C (1-propanol); ir: 3387,3336 cm^{-1} (NH), 1676 cm^{-1} (C=O), 1625 cm^{-1} (C=O).

Anal. Calcd. for $C_{29}H_{20}N_4O_4$: C, 71.30; H, 4.13; N, 11.47. Found: C, 71.42; H, 4.14, N, 11.45.

N-[4-Benzoyl-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl]-*N'*-phenylurea (**5d**).

a) Compound **5d** was prepared by the general procedure above with a reflux time of 4 hours (phenylurea) resulting in a yield of 45% (0.239 g); mp 214 °C (1-propanol); ir : 3397, 3250 cm^{-1} (NH), 1753 cm^{-1} (C=O, urea), 1676 cm^{-1} (C=O) 1625 cm^{-1} (C=O); ^{13}C-nmr (deuteriochloroform): δ 192.42 (C=O), 162.75

(C=O), 151.92 (C=O, urea), 150.42 (C-NO_2), 146.64 (C-3), 145.49 (C-5), 141.33 (N-PhNO_2), 139.19 (N-Ph), 139.03 (C-Ph), 135.87, 132.40, 132.22, 131.61, 131.52, 131.17, 130.94, 130.65, 128.74 (C-Ph), 126.37, 125.37, 122.36, 122.05 ppm (C-4).

Anal. Calcd. for $C_{30}H_{21}N_5O_5$: C, 67.79; H, 3.98; N, 13.18. Found: C, 68.02; H, 3.97, N, 13.21.

b) The acid amide **5a** (0.412 g, 1 mmole) and phenylisocyanate (0.2 ml, 1,8 mmoles) were refluxed in xylene for 5 hours. Then the solvent was evaporated and the residue was recrystallized from 1-butanol to give 0.4 g (75%) of **5d**, identical in mp and ir spectrum with that product obtained as described above.

N-[4-Benzoyl-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl]-*N'*-ethylurea (**5e**).

Compound **5e** was prepared by the general procedure above with a reflux time of 4 hours (ethyl urea) resulting in a yield of 48% (0.232 g); mp 195 °C (1-propanol); ir: 3362 cm^{-1} (NH), 1702 cm^{-1} (C=O, urea), 1676 cm^{-1} (C=O), 1625 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 8.87 (s, 1H, NH), 8.28-7.15 (m, 14H, ArH), 3.32 (m, 2H, N-CH_2), 1.63 (b, C-NH), 1.15 ppm (t, 3H, CH_3).

Anal. Calcd. for $C_{26}H_{21}N_5O_5$: C, 64.59; H, 4.38; N, 14.49. Found: C, 64.66; H, 4.39, N, 14.47.

N-[4-Benzoyl-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl]-*N'*-benzylurea (**5f**).

Compound **5f** was prepared by the general procedure above with a reflux time of 4 hours (benzyl urea) resulting in yield 0.3 g (55%), mp 212 °C (1-butanol); ir: 3361-3336 cm^{-1} (NH), 1727 cm^{-1} (C=O, urea), 1676 cm^{-1} (C=O), 1625 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 8.96 (s, 1H, NH), 8.43 (t, 1H, NH), 8.28-7.15 (m, 19H, ArH), 4.48 ppm (d, 2H, CH_2).

Anal. Calcd. for $C_{31}H_{23}N_5O_5$: C, 68.25; H, 4.25; N, 12.84. Found: C, 68.37; H, 4.24, N, 12.80.

4-Benzoyl-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonitrile (**6**).

A cold solution of the acid amide **5a** (0.412 g, 1 mmole) in a mixture of DMF (0.7 ml) and $SOCl_2$ (0.15 ml) was stirred at 0-5 °C for 2 hours. After heating to room temperature, stirring was continued overnight, then the reaction mixture was poured over crushed ice and the separated solid isolated by filtration, washed with water and crystallized from 1-propanol to give 0.229 g (58%) of **6** mp 190 °C; ir: 2263 cm^{-1} (CN), 1676 cm^{-1} (C=O); ^{13}C-nmr (deuteriochloroform): δ 189.81 (C=O), 150.37 (C-NO_2), 147.56 (C-3), 141.05 (C-5), 138.43 (N-PhNO_2), 135.62, 132.81, 132.45, 132.26, 132.14, 131.59, 131.02, 130.39, 129.63 (C-Ph), 128.28 (C-Ph), 127.32 (C-4), 125.72, 122.47, 113.99 ppm (CN).

Anal. Calcd. for $C_{23}H_{14}N_4O_3$: C, 70.05; H, 3.58; N, 14.21. Found: C, 70.25; H, 3.57, N, 14.18.

1-(3-Aminophenyl)-4-benzoyl-5-phenyl-1*H*-pyrazole-3-carboxylic Acid (**7**)**.**

A cold solution of sodium polysulphide (10 mmoles), prepared from $Na_2S{\bullet}9H_2O$ (2.5 g, 10 mmoles) with powdered sulphur (0.7 g) in boiling water, was added into the solution of **2** (4.13 g, 10 mmoles) in methanol with stirring. The reaction mixture was refluxed on a steam-bath for 60 minutes. After cooling and acidification with concentrated HCl, it was refluxed again for 30 minutes to precipitate sulphur, cooled and the seperated solid was filtered off. Then, the filtrate was made alkaline by adding concentrated aqueous ammonia (slight excess) and kept in refrigerator over-night. The crude precipitate was washed with water and recrystallized from ethanol to give 2.49 g (65%) of **7** mp 181 °C; ir: 3384 cm^{-1} (NH_2), 3258-2700 cm^{-1} (b, OH, COOH), 1709 cm^{-1} (C=O, COOH), 1667 cm^{-1} (C=O, benzoyl). ^{1}H-nmr (deuteriochloroform): δ 7.69-6.39 ppm (m, 14H, ArH), 5.76 ppm (b, NH_2). ^{13}C-nmr (deuteriochloroform): δ 194.85 (C=O), 164.61 (COOH), 147.26 (H_2N-Ph), 144.67 (C-3), 141.37 (C-5), 139.41 (N-PhNH_2), 135.19, 131.97, 131.64 (C-Ph), 131.50, 131.33, 130.39, 130.17, 129.77 (C-Ph), 124.00, 117.91, 117.74, 114.63 (C-4), 114.47 ppm.

Anal. Calcd. for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 72.23; H, 4.48, N, 10.93.

2-(3-Nitrophenyl)-3,4,6-triphenyl-2,6-dihydropyrazolo-[3,4-*d*]-pyridazin-7-one (**8a**).

General Procedure.

A milliequimolar mixture of **2** and phenylhydrazine was refluxed in xylene for 3 hours. After the solvent was removed by evaporation, the oily residue was treated with ether and the formed crude product was recrystallized from methanol.

Compound **8a** was obtained in 58% yield (0.28 g); mp 186 °C; ir: 1687 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 8.24-6.87 ppm (m, 19H, ArH); ^{13}C-nmr (DMSO-d_6): δ 157.32 (C=O), 150.18 (C-NO_2), 145.95 (C-7a), 143.66 (C-4), 142.59 (C-3), 141.82 (N-PhNO_2), 135.79 (N-Ph), 133.50, 132.37, 132.23 (C-Ph), 132.15 (C-Ph), 132.00, 131.77, 130.73, 130.66, 130.59, 129.72, 129.61, 129.23, 127.99, 125.56, 123.09, 119.09 ppm (C-3a).

Anal. Calcd. for $C_{29}H_{19}N_5O_3$: C, 71.74; H, 3.94; N, 14.42. Found: C, 72.01; H, 3.93, N, 14.40.

2-(3-Nitrophenyl)-3,4-diphenyl-2,6-dihydropyrazolo-[3,4-*d*]-pyridazin-7-one (**8b**)**.**

Compound **8b** was prepared according to the general procedure above with a reflux time of 1 hour (hydrazinehydrate) resulting in 55% yield (0.225 g); mp 302 °C (isopentyl alcohol); ir :3300-2750 cm^{-1} (b, NH⇆OH), 1679.3 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 12.64 (b, 1H, OH), 8.29-6.99 ppm (m, 14H, ArH); ^{13}C-nmr (DMSO-d_6): δ 157.75 (C=O), 149.41 (C-NO_2), 145.31 (C-7a), 144.29 (C-4), 142.53 (C-3), 141.29 (N-PhNO_2), 135.92, 134.21, 132.45, 132.35, 131.04 (C-Ph), 130.08, 129.98 (C-Ph), 129.98, 129.13, 125.60, 123.00, 118.63 ppm (C-3a).

Anal. Calcd. for $C_{23}H_{15}N_5O_3$: C, 67.48; H, 3.69; N, 17.11. Found: C, 67.54; H, 3.68, N, 17.15.

2-(3-Aminophenyl)-3,4,6-triphenyl-2,6-dihydropyrazolo-[3,4-*d*]pyridazin-7-one (**8c**).

a) Compound **8c** was prepared according to the general procedure above with a reflux time of 4 hours (phenylhydrazine) resulting in 45% yield (0.205 g); mp 253 °C (1-butanol); ir: 3453-3358 cm^{-1} (NH_2), 1685.43 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 7.77-6.42 (m, 19H, ArH), 3.79 ppm (b, 2H, NH_2); ^{13}C-nmr (deuteriochloroform): δ 157.72 (C=O), 149.47 (C-NH_2), 146.23 (C-7a), 145.08 (C-4), 143.91 (C-3), 141.97 (N-Ph), 141.78 (N-PhNH_2), 136.23, 132.42, 131.51 (C-Ph), 131.31, 131.13 (C-Ph), 130.96, 130.63, 130.49, 130.04, 129.62, 129.43, 128.28, 118.51 (C-3a), 117.60, 117.49, 114.59 ppm.

Anal. Calcd. for $C_{29}H_{21}N_5O$: C, 76.47; H, 4.65; N, 15.37. Found: C, 76.40; H, 4.66, N, 15.34.

b) Compound **8a** (0.485 g, 1 mmole) and Na_2S_X (1 mmole) were refluxed in a mixture of ethanol and water on a steam-bath for about 60 minutes. The crude product which precipitated in boiling solvents was isolated by filtration and recrystallized from a mixture of methanol and water to give 0.25 g (55%) of **8c**, identical in mp and ir spectrum with that product obtained as described above.

2-(3-Aminophenyl)-3,4-diphenyl-2,6-dihydropyrazolo-[3,4-*d*]-pyridazin-7-one (**8d**).

Compound **8d** was prepared according to the general procedure above with a reflux time of 4 hours (hydrazinehydrate) resulting in a 40% yield (0.152 g); mp 301 °C (ethanol); ir: 3437.5-3344.2 cm^{-1} (NH_2) 3300-2750 cm^{-1} (b, NH⇆OH), 1668.43 cm^{-1} (C=O); ^{13}C-nmr (DMSO-d_6): δ 157.99 (C=O), 151.19 (C-NH_2), 145.44 (C-7a), 143.49 (C-4), 141.61 (C-3), 141.38 (N-PhNH_2), 136.16, 132.19, 130.78 (C-Ph), 130.53 (C-Ph), 130.06, 129.83, 129.75, 129.45, 129.08, 118.19 (C-3a), 116.17, 115.07, 113.14 ppm.

Anal. Calcd. for $C_{23}H_{17}N_5O$: C, 72.81; H, 4.52; N, 18.46. Found: C, 72.68; H, 4.51, N, 18.51.

2-(3-Nitrophenyl)-3,4-diphenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7-yl-amine (**9**).

Compound **6** (0.394 g, 1 mmole) and anhydrous hydrazine (0.032 g, 1 mmole) were refluxed in 1-butanol containing a catalytic amount of metallic sodium on an oil-bath for 8 hours. The precipitate formed in boiling 1-butanol was isolated by filtration and recrystallized from methanol to give 0.143 g (35%) of **9**, mp 281 °C; ir: 3483-3182 cm^{-1} (NH), 1683 cm^{-1} (C=NH); ^{13}C-nmr (DMSO-d_6): δ 157.84 (C=NH), 145.41 (C-NO_2), 145.08 (C-7a), 142.25 (C-3), 140.88 (N-PhNO_2), 135.93 (C-4), 132.41, 131.70 (C-Ph), 131.34, 131.04, 130.90 (C-Ph), 130.08, 129.69, 129.68, 129.14, 129.00, 128.95, 127.98, 122.00 ppm (C-3a).

Anal. Calcd. for $C_{23}H_{16}N_6O_2$: C, 67.64; H, 3.95; N, 20.58. Found: C, 67.55; H, 3.95, N, 20.53.

1-(3-Nitrophenyl)-5-phenyl-4-[phenyl-(pyridin-2-yl-hydrazono)-methyl]-1*H*-pyrazole-3-carboxylic Acid (**10**).

Compound **2 (**0.413 g, 1 mmole) and 0.109 g (1 mmole) of 2-hydrazinopyridine were refluxed in xylene on an oil-bath for 4 hours. The solvent was evaporated and the remaining oily residue was treated with ether to give a crude product which was recrystallized from ethanol, yield 0.479 g (95%), mp 231 °C (decomp.); ir: 3437.53 cm^{-1} (NH), 1651.25 cm^{-1} (C=N-), 1609.1, 1576.33 (COO); ^{1}H-nmr (deuteriochloroform): δ 10.20 (b, acidic proton), 8.92 (b, 1H, NH), 8.18-6.57 ppm (m, 18H, ArH); ^{13}C-nmr (deuteriochloroform): δ 167.06 (COO), 157.90 (C-2', pyr.), 149.64 (C-NO_2), 146.13 (C=N-), 145.56 (C-3), 145.10 (C-6', pyr.), 143.34 (C-5), 142.86, 141.49 (N-PhNO_2), 141.12, 136.08, 136.01, 131.37, 131.28 (C-Ph), 131.21, 130.65, 130.24, 130.11 (C-Ph), 128.57, 124.42, 122.74, 116.94, 116.60, 111.44 ppm (C-4).

Anal. Calcd. for $C_{28}H_{20}N_6O_4$: C, 66.66; H, 4.00; N, 16.66. Found: C, 66.47; H, 4.01, N, 16.69.

[1-(3-Nitrophenyl)-5-phenyl-1*H*-pyrazol-4-yl](phenyl)-methanone-*N*-pyridin-2-yl Hydrazone (**11**).

Compound **10** (0.46 g, 1 mmole) was heated to 235-240 °C on an oil-bath for about 30 minutes without any solvent. After cooling to room temperature, the residue was treated with ether to give crude product which was recrystallized from ethanol, yield 0.23 g (50%), mp 239 °C; ir: 3361 cm^{-1} (NH), 1676 cm^{-1} (C=N); ^{13}C-nmr (deuteriochloroform): δ 156.83 (C-2', pyr.), 154.73 (C=N-), 150.69 (C-6', pyr.), 149.52 (C-NO_2), 145.74 (C-3), 145.08 (C-5), 142.15, 141.09 (C-PhNO_2), 139.33, 134.93 (C-Ph), 132.79, 131.65, 131.30, 131.05, 130.00, 129.93, 129.00, 128.43 (C-Ph), 124.89, 124.69, 123.28, 122.38, 118.67 ppm (C-4).

Anal. Calcd. for $C_{27}H_{20}N_6O_2$: C, 70.42; H, 4.38; N, 18.25. Found: C, 70.53; H, 4.39; N, 18.20.

2-(3-Nitrophenyl)-3,4-diphenylpyrazolo[4,3-*d*][1,2]oxazin-7(2*H*)-one (**12**).

Pyrazole acid **2** (0.413 g, 1 mmole) and a large excess of hydroxylamine hydrochloride were heated to about 150-155 °C on an oil-bath for approximately 30 minutes, until of sublimation of excess hydroxylamine hydrochloride ceased, with stirring. After cooling to room temperature, the resulting mixture was first washed with water then treated with ether, the crude product which was formed in this way was recrystallized from a mixture of ethanol and water to give 0.267 g (65%) of pure **12**, mp 149 °C; ir: 1696 cm^{-1} (C=O); ^{13}C-nmr (deuteriochloroform): δ 161.33 (C=O), 149.65 (C-NO_2), 143.90 (C-7a), 143.09 (C-4), 141.33 (C-3), 138.93 (N-PhNO_2), 133.32 (C-Ph), 132.20, 131.99, 131.75, 131.45, 131.18, 130.25, 129.44 (C-Ph), 125.59, 123.67, 121.00, 120.90, 120.52 (C-3a).

Anal. Calcd. for $C_{23}H_{14}N_4O_4$: C, 67.31; H, 3.44; N, 13.65. Found: C, 67.11; H, 3.44, N, 13.64.

2-(2-Methylquinolin-7-yl)-3,4-diphenyl-2,6-dihydropyrazolo-[3,4-*d*]-pyridazin-7-one **(13a).**

General Procedure.

To the cold solution of compound **8d** (1 mmole) in concentrated HCl (15-20 ml) was added acetaldehyde (0.1 ml, 2 mmoles) and nitrobenzene (0.123 g, 1 mmole), with stirring and the stirring continued at room temperature for 60 minutes. Then, the reaction mixture was refluxed on a steam-bath for 12 hours with stirring and filtered. The filtrate was made alkaline by adding concentrated aqueous ammonia and kept in a refrigerator overnight. The separated solid was isolated by filtration, washed with water and recrystallized from acetone. The yield 0.193 g (45%), mp 287 °C; ir: 3435.52 cm^{-1} (NH⇆OH), 1673.48 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 12.68 (b, NH⇆OH), 8.30 (d, J=8.4 Hz, 1H, H-4'), 8.00 (d, J=8.8 Hz, 1H, H-6'), 7.91 (m, 1H, J<2, H-8'), 7.73-6.80 (m, 12H, ArH), 2.64 ppm (s, 3H, CH_3); ^{13}C-nmr (DMSO-d_6): δ 162.30 (C=O), 157.94 (C-2'), 148.23 (C-8'a), 145.43 (C-7a), 144.00 (C-4), 142.39 (C-3), 140.99 (N-Quin), 137.82, 136.03, 132.39 (C-Ph), 131.99 (C-Ph), 130.79, 130.62, 130.07, 129.65, 129.51, 129.14, 127.71, 127.29, 125.44, 25.22, 118.54 (C-3a), 26.52 ppm (CH_3).

Anal. Calcd. for $C_{27}H_{19}N_5O$: C, 75.51; H, 4.46; N, 16.31. Found: C, 75.78; H, 4.44, N, 16.28.

2-(2-Methylquinolin-7-yl)-3,4,6-triphenyl-2,6-dihydropyrazolo[3,4-*d*]pyridazin-7-one (**13b**).

Compound **13b** was prepared according to the general procedure above with a reflux time of 8 hours resulting in 40% yield (0.2 g); mp 265 °C (methanol); ir: 1676 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 8.05 (d, J=8.4 Hz, 1H, H-4'), 7.98 (d, J=9.2 Hz, 1H, H-8'), 7.88 (m, J<2 Hz, 1H, H-6'), 7.74-6.90 ppm (m, 17H, ArH), 2.69 ppm (s, 3H, CH_3); ^{13}C-nmr (deuteriochloroform): δ 162.50 (C=O), 157.70 (C-2'), 149.44 (C-8'a), 146.24

(C-7a), 145.06 (C-4), 143.87 (C-3), 141.96 (N-Quin), 141.78 (N-Ph), 136.18, 135.73, 132.51 (C-Ph), 132.41, 131.33, 131.18, 130.96, 130.62, 130.50, 130.29, 130.04 (C-Ph), 129.87, 129.62, 129.44, 128.08, 125.28, 117.61, 114.55 ppm (C-3a), 27.32 ppm (CH_3).

Anal. Calcd. for $C_{33}H_{23}N_5O$: C, 78.40; H, 4.59; N, 13.85. Found: C, 78.61; H, 4.58, N, 13.88.

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