# Pyrazoles as Building Blocks in Heterocyclic Synthesis: Synthesis of Some New Substituted 1-Triazinylpyrazolo[3,4-*d*]pyrimidine and 1-Triazinylpyrazolo[3,4-*b*]pyridine Derivatives

A.-F. A. HARB*, H. H. ABBAS, and F. H. MOSTAFA

*Department of Chemistry, Faculty of Science (Qena), South Valley University, Qena, 83523, Egypt*
*e-mail: funnytostos@hotmail.com*

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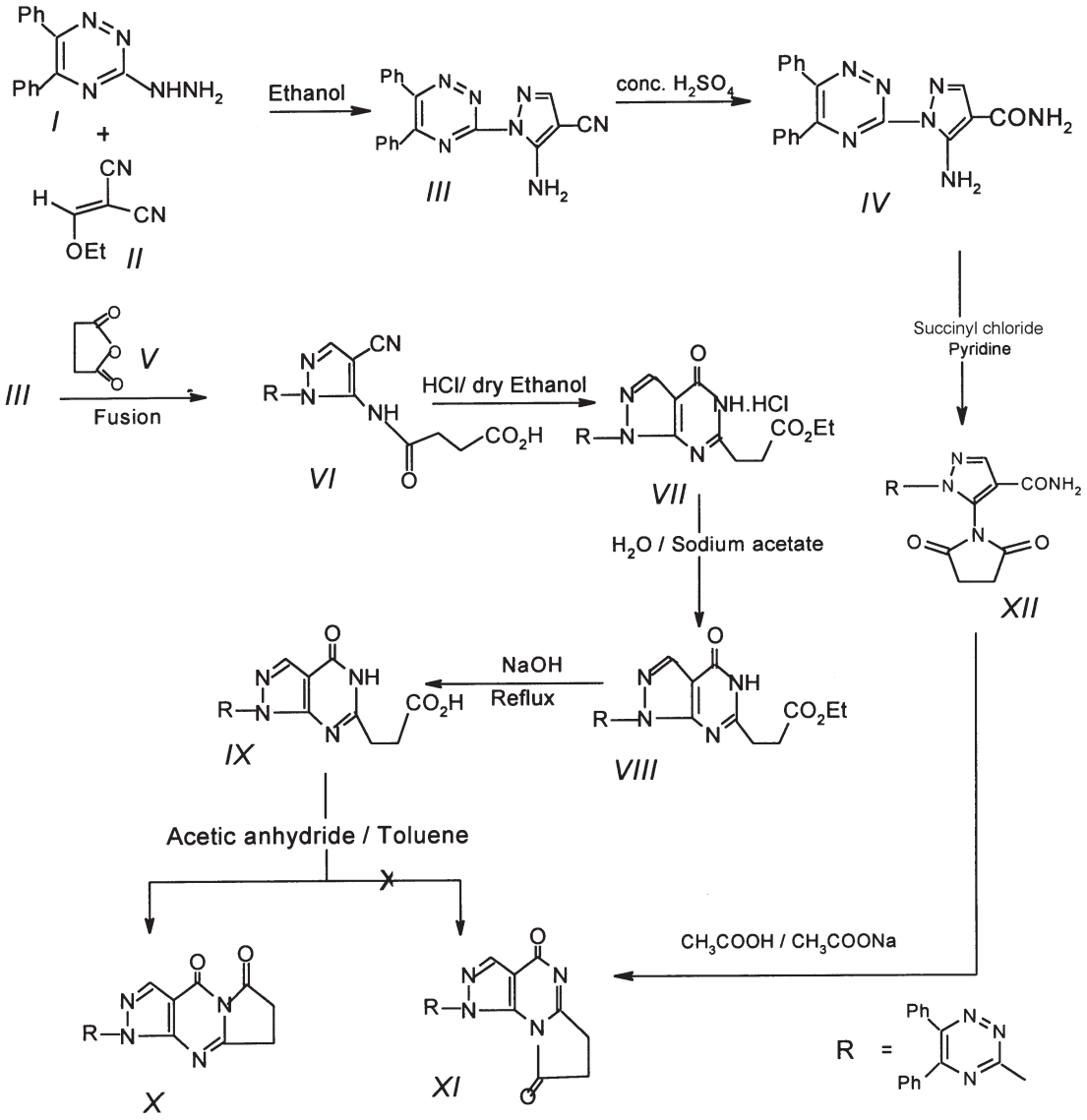
Several new pyrazolo[3,4-*d*]pyrimidines and pyrazolo[3,4-*b*]pyridine derivatives were prepared by condensation of 5-amino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazole-4-carbonitrile with succinic anhydride, acetic anhydride, $\gamma$-chlorobutyl chloride, succinyl chloride, formic acid—formamide mixture, formamide, and active methylene reagents such as malononitrile, ethyl cyanoacetate, and ethyl acetoacetate under different reaction conditions.

Azoloazines are biologically interesting molecules and their chemistry is now receiving considerable attention [1—3]. Also, the considerable biological activities of pyrazole, pyridine, and their annulated derivatives as antimycotic [4], antidepressant [5], fungicidal [6], and herbicidal [7] agents stimulated our interest in the synthesis of several new derivatives of these ring systems. Thus, 5-amino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazole-4-carbonitrile (*III*) was prepared as a starting compound in the present work, by reaction of the known 3-hydrazino-5,6-diphenyl-1,2,4-triazine (*I*) [8] with ethoxymethylenemalononitrile (*II*) in refluxing ethanol in a good yield (Scheme 1). Acid hydrolysis of compound *III* using cold concentrated sulfuric acid followed by neutralization with ammonium hydroxide afforded the corresponding carboxamide derivative *IV*. Structures *III* and *IV* as well as other synthesized compounds were confirmed on the basis of their elemental and spectral data. Thus, IR spectra exhibit the absence of the characteristic stretching vibration due to —CN group in case of product *IV*, but revealed the presence of —CN group characteristic stretching vibrations at $\tilde{\nu}$ = 2225 cm$^{-1}$ in case of *III*. Also, the $^1$H NMR spectra showed the presence of signals due to an amino group at $\delta$ = 5.38 in case of product *III*, and at $\delta$ = 8.61 and $\delta$ = 5.49 due to carboxamido and amino groups, respectively. In addition, the mass spectra revealed ion peak at *m/z* = 339.12 in case of product *III*, and at *m/z* = 357.11 in case of product *IV*.

By fusion of compound *III* with freshly prepared succinic anhydride (*V*), the corresponding acid *VI* was obtained. The mass spectrum showed ion peak at *m/z* = 439. IR spectrum revealed in addition to the presence of the stretching vibrations at $\tilde{\nu}$ = 2220 cm$^{-1}$ due to —CN group, the presence of the stretching vibrations at $\tilde{\nu}$ = 3400—3100 cm$^{-1}$, $\tilde{\nu}$ = 1675 cm$^{-1}$, and $\tilde{\nu}$ = 1655 cm$^{-1}$ due to —NHCO— and —COOH groups. Also, the $^1$H NMR showed besides the presence of the characteristic signals at $\delta$ = 12.75 and $\delta$ = 9.74 due to —COOH and —NHCO— groups, the presence of characteristic signals at $\delta$ = 4.13 and $\delta$ = 3.86 due to two —$CH_2$— groups.

Treatment of *VI* with dry hydrogen chloride in anhydrous ethanol afforded the corresponding chloride salt of the ethyl $\beta$-(pyrazolo[3,4-*d*]pyrimidinone)propionate *VII*. Treatment of *VII* with aqueous sodium acetate gave rise to the free ethyl $\beta$-(pyrazolo[3,4-*d*]pyrimidinone)propionate *VIII*. Mass spectrum showed ion peak at *m/z* = 467. IR spectrum revealed in addition to the presence of two stretching vibrations at $\tilde{\nu}$ = 1665 cm$^{-1}$ and $\tilde{\nu}$ = 1690 cm$^{-1}$ due to amidic and hydrogen-bonded ester carbonyl groups, the absence of the stretching vibration at $\tilde{\nu}$ = 2220 cm$^{-1}$ due to the cyano function of compound *VI*. Also, the $^1$H NMR spectrum showed the presence of characteristic quartet, triplet signals at $\delta$ = 4.33 and $\delta$ = 1.55 due to ethyl ester group. On the other hand, alkaline hydrolysis of *VIII* using 10 % aqueous NaOH, gave in good yield the corresponding $\beta$-(pyrazolo[3,4-*d*]pyrimidinone)propanoic acid derivative having structure *IX*. The $^1$H NMR spectrum showed the absence of the characteristic quartet, triplet signals at $\delta$ = 4.33 and $\delta$ = 1.55 due

*The author to whom the correspondence should be addressed.



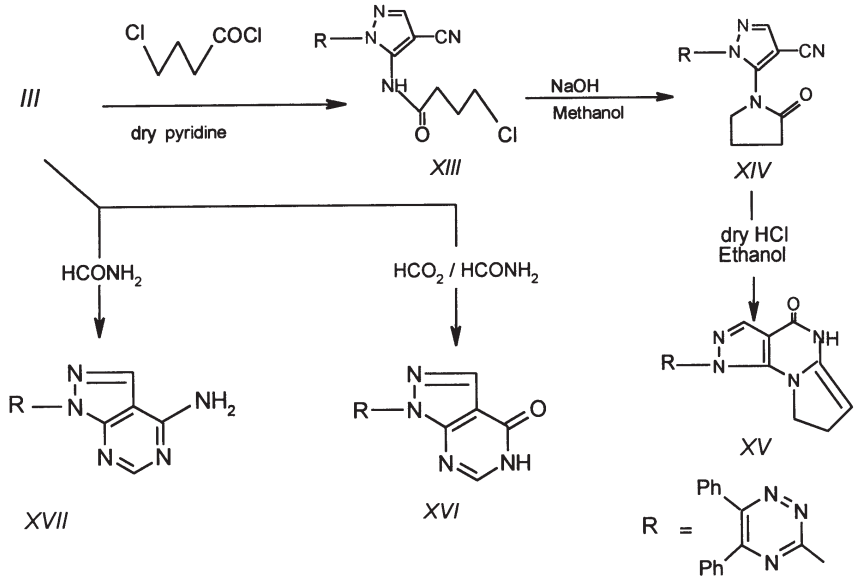

*Scheme 1*

to ethyl ester group. However, the characteristic signal at $\delta = 12.52$ due to —COOH group appeared.

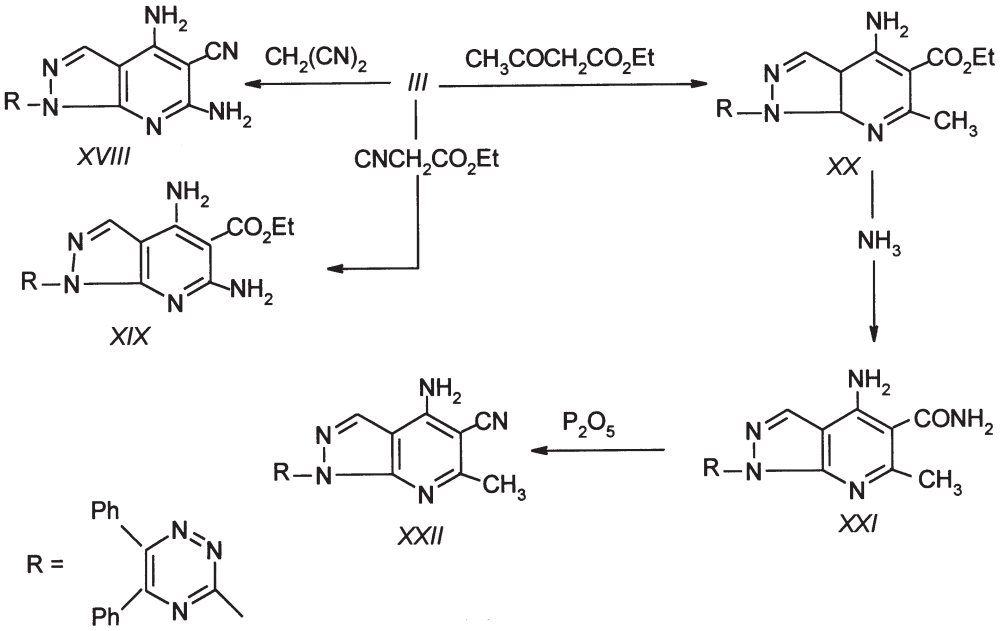
Hoping to effect a dehydrating cyclization of *IX* in a manner analogous to that previously described by *Taylor* [9—11], we heated compound *IX* under reflux in acetic anhydride—toluene mixture. A product having molecular formula $C_{23}H_{15}N_7O_2$ ($m/z = 421$) was obtained. The elemental and spectral analysis of the isolated product is consistent with both structures *X* and *XI* (*cf.* Experimental). However, structure *X* was suggested for the reaction product and not structure *XI* by preparing compound *XI* from reaction of compound *IV* with succinyl chloride in dry pyridine *via* intermediacy of compound *XII*. Its mass spectrum showed ion peak at $m/z = 439$, the $^1$H NMR showed the presence of the characteristic signals at $\delta = 8.34$ and $\delta = 4.21$ due to —$CONH_2$ and two —$CH_2$— groups, respectively. IR spectrum revealed the presence of the characteristic stretching vibrations at $\tilde{\nu} =$ 1658—1645 cm$^{-1}$ due to amidic carbonyl groups.

On the other hand, 4-chloro-*N*-[4-cyano-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazol-5-yl]butyramide (*XIII*) was formed by condensation of compound *III* with 4-chlorobutyryl chloride in dry pyridine (Scheme 2). The mass spectrum showed ion peaks at $m/z = 443.13$ (100 %). The $^1$H NMR showed the presence of the characteristic signals at $\delta = 8.13$ due to NH and $\delta = 4.38$, $\delta = 3.17$, and $\delta = 1.97$ due to three —$CH_2$— groups.

Treating of *XIII* with sodium hydroxide in aqueous methanol at room temperature afforded 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-5-(2-oxopyrrolidin-1-yl)-1*H*-pyrazole-4-carbonitrile (*XIV*). The mass spectrum showed ion peak at $m/z = 407.15$ (100 %). IR spectrum revealed in addition to the presence of the stretching vibration at $\tilde{\nu} = 2220$ cm$^{-1}$ due



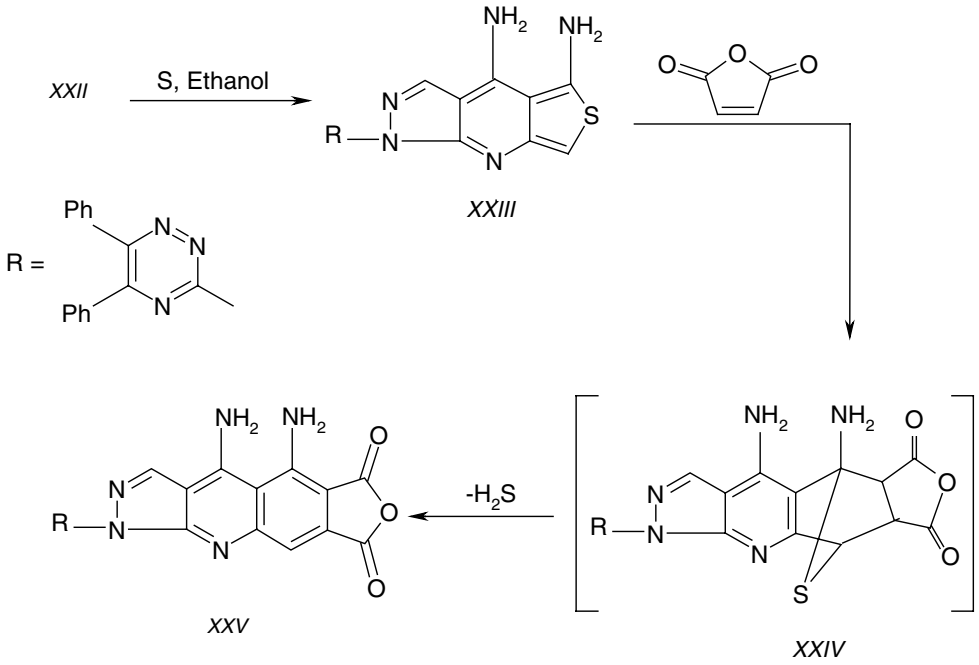

*Scheme 2*




*Scheme 3*

to the cyano function, the presence of stretching vibration at $\tilde{\nu} = 1700$ cm$^{-1}$ due to carbonyl group. Also, the $^1$H NMR spectrum showed the presence of characteristic signals at $\delta = 4.41$ and $\delta = 3.35$, and $\delta = 2.25$ due to three methylene groups. Compound *XIV* was cyclized to the corresponding 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-7,8-dihydro-1*H*-pyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrimidin-4(5*H*)-one (*XV*) using dry hydrogen chloride in absolute ethanol. The mass spectrum showed ion peak at $m/z = 407.18$ (100 %). IR spectrum revealed in addition to the disappearance of the stretching vibration at $\tilde{\nu} = 2220$ cm$^{-1}$ due to the cyano function, the appearance of the stretching vibration at $\tilde{\nu} = 1680$ cm$^{-1}$ due to amidic carbonyl group. Also, the $^1$H NMR spectrum showed the presence of signals at $\delta = 8.12$, $\delta = 4.62$, $\delta = 3.12$, and $\delta = 2.88$ due to >NH, —CH—, and two —$CH_2$— groups, respectively.

On heating of compound *III* with equimolar mixture of formic acid and formamide, or with formamide only, the corresponding 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (*XVI*), and 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (*XVII*) were obtained, respectively. The IR spectrum of *XVI* showed the presence of the stretching vibration at $\tilde{\nu} = 1680$ cm$^{-1}$




*Scheme 4*

due to amidic carbonyl group, which was replaced by the characteristic stretching vibrations of the amino group at $\tilde{\nu} = 3500$—$3330$ cm$^{-1}$ in the IR spectrum of *XVII*. Also, the $^1$H NMR spectrum of *XVI* showed the presence of signals of only one NH proton at $\delta = 9.94$. However, the $^1$H NMR spectrum of *XVII* showed the presence of signals due to tow protons of —$NH_2$ group at $\delta = 5.24$.

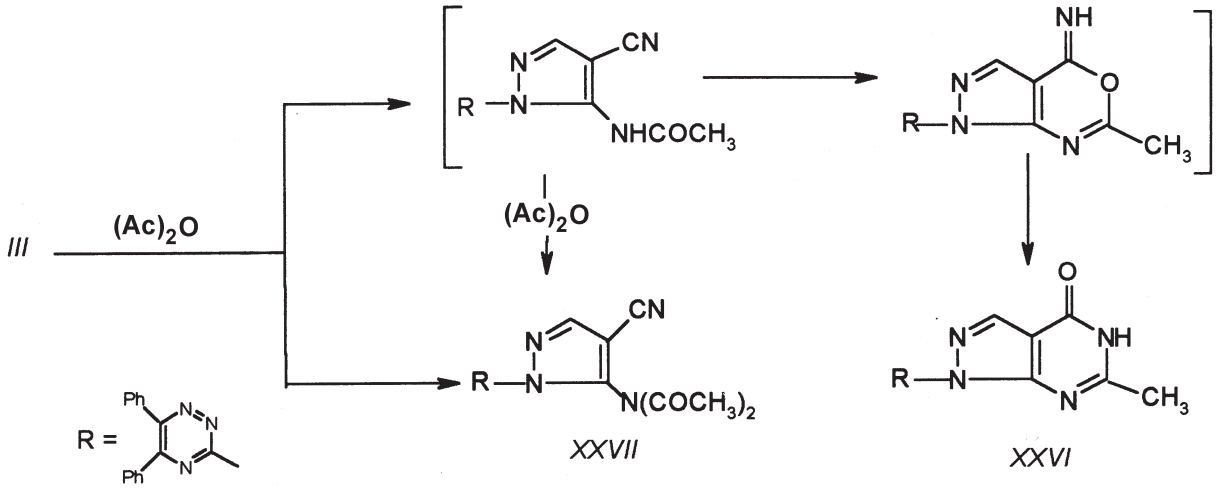
By heating of *III* with malononitrile in *o*-dichlorobenzene in the presence of $TiCl_4$ as a catalyst the corresponding 4,6-diamino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile *XVIII* was obtained (Scheme 3). Under similar conditions, interaction of compound *III* with ethyl cyanoacetate and ethyl acetoacetate afforded the corresponding ethyl 4,6-diamino- *XIX* and ethyl 4-amino-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate derivative *XX*, respectively. The IR spectra in all cases revealed the presence of the stretching vibrations at $\tilde{\nu} = 3500$—$3200$ cm$^{-1}$ due to the amino groups. Also, they revealed the presence of the stretching vibrations at $\tilde{\nu} = 2220$ cm$^{-1}$ due to the CN function in case of *XVIII*. However, in case of *XIX* and *XX* the stretching vibrations at $\tilde{\nu} = 1680$—$1675$ cm$^{-1}$ due to the ester carbonyl groups appeared. Also, the $^1$H NMR spectra of *XIX* and *XX* showed the presence of signals of the ethyl ester groups protons at $\delta = 4.11$ and $\delta = 1.17$ in case of *XIX* and at $\delta = 4.14$ and $\delta = 1.22$ in case of *XX*. However, the $^1$H NMR spectrum of *XVIII* showed the presence of signals due to four protons of two —$NH_2$ groups at $\delta = 6.13$.

Stirring of compound *XX* with ammonia solution at room temperature afforded the corresponding pyrazolo[3,4-*b*]pyridine-5-carboxamide *XXI* in quantitative yield. By fusion of *XXI* with $P_2O_5$ for 1 h, the corresponding pyrazolo[3,4-*b*]pyridine-5-carbonitrile *XXII* was obtained. The IR spectrum of *XXI* revealed the presence of the characteristic stretching vibration at $\tilde{\nu} = 1655$ cm$^{-1}$ due to the 5-carboxamido group, which was replaced by stretching vibration at $\tilde{\nu} = 2216$ cm$^{-1}$ due to 5-CN group in case of *XXII*.

Reaction of *XXII* with elemental sulfur in refluxing ethanolic piperidine solution affords the corresponding 1*H*-pyrazolo[3,4-*b*]thieno[3,4-*e*]pyridine-4,5-diamine derivative *XXIII* (Scheme 4), spectral data of which showed the disappearance of the characteristic stretching vibrations at $\tilde{\nu} = 2216$ cm$^{-1}$ due to —CN group. The $^1$H NMR spectrum revealed also the disappearance of the characteristic signal due to the methyl group at $\delta = 2.61$. However, new characteristic stretching vibrations at $\delta = 6.71$ due to one amino group besides the original amino group stretching vibrations at $\delta = 5.62$ appeared.

A fission of *XXIII* with maleic anhydride gave the corresponding 4,5-diamino-1*H*-pyrazolo[3,4-*b*]furo[3,4-*g*]quinoline-6,8-dione derivative *XXV*. Structure of *XXV* was established on the basis of the suitable elemental microanalysis which revealed the absence of sulfur. Also, the mass spectrum showed ion peak at $m/z = 500$. IR spectrum revealed also, in addition to the presence of the amino group stretching vibrations in the 3400 cm$^{-1}$ region, the presence of two carbonyl groups stretching vibrations at $\tilde{\nu} = 1780$—$1720$ cm$^{-1}$. The formation of *XXV* is assumed to proceed *via* initial [4 + 2] cycloaddition of the olefinic $\pi$-bond to diene system of *XXIII* yielding the cycloadduct intermediate *XXIV* which, followed by hydrogen sulfide elimination, gives the final product *XXV*.

Refluxing of compound *III* in acetic anhydride for




*Scheme 5*

3 h not only gave the corresponding pyrazolo[3,4-*d*]pyrimidinone derivative *XXVI* but also the corresponding *N,N*-diacetylpyrazole derivative *XXVII* was isolated from the reaction media as a by-product (Scheme 5). The IR spectra exhibited the absence of the characteristic stretching vibrations due to CN group in case of product *XXVI*, but revealed the characteristic stretching vibrations at $\tilde{\nu} = 2220$ cm$^{-1}$ due to —CN group in case of product *XXVII*. Also, the $^1$H NMR spectra showed the presence of signals due to only one methyl group at $\delta = 2.42$ in case of product *XXVI*, and at $\delta = 3.17$ due to two methyl groups in case of product *XXVII*. In addition, the mass spectra revealed ion peaks at $m/z = 381$ in case of product *XXVI*, and at $m/z = 423$ in case of product *XXVII*.

## EXPERIMENTAL

All melting points were uncorrected. The microanalytical unit at the Cairo University measured microanalytical data. IR (KBr) spectra were recorded on Shimadzu 408 spectrophotometer. Mass spectra were taken on GCMS QP1000 Ex mass spectrometer with ionization potential of 70 eV. $^1$H NMR spectra were measured on a 90 MHz Varian EM-390 spectrometer with hexadeuterodimethyl sulfoxide as solvent, using $Me_4Si$ as an internal standard.

### 5-Amino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazole-4-carbonitrile (*III*)

A mixture of 3-hydrazino-5,6-diphenyl-1,2,4-triazine (*I*) (13.2 g; 0.05 mol) and ethoxymethylenemalononitrile (*II*) (6.1 g; 0.05 mol) in absolute ethanol (100 cm$^3$) was heated under reflux for 1 h. The reaction mixture was concentrated and allowed to cool. The separated pale yellow crystals from *III* were collected by suction. Yield = 13.8 g (80 %), m.p. = 250 °C (ethanol). For $C_{19}H_{13}N_7$ ($M_r = 339.35$) $w_i$(calc.): 67.25 % C, 3.86 % H, 28.89 % N; $w_i$(found): 67.37 % C, 3.98 % H, 29.13 % N. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 3400—3300 $\nu$(NH$_2$), 2225 $\nu$(CN). Mass spectrum, $m/z$ ($I_r$/%): 339.12 (100), 340.13 (21).

### 5-Amino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-pyrazole-4-carboxamide (*IV*)

To cold $H_2SO_4$ (100 cm$^3$) in ice bath, *III* (3.39 g; 0.01 mol) was added with stirring. The mixture was stirred at room temperature for 5 h. The dark reaction mixture was then poured onto crushed ice and the solution was neutralized with concentrated ammonium hydroxide. The reaction mixture, which was allowed to reach 65—70 °C during neutralization, was cooled to room temperature and filtered to give a yellow precipitate which crystallized as yellow crystals. Yield = 2.8 g (79.5 %), m.p. = 157 °C (ethanol). For $C_{19}H_{15}N_7O$ ($M_r = 357.37$) $w_i$(calc.): 63.86 % C, 4.23 % H, 27.44 % N; $w_i$(found): 64.07 % C, 3.93 % H, 27.72 % N. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 3400—3200 $\nu$(NH$_2$ and CONH$_2$) and 1655 $\nu$(CO).

### 4-{[4-Cyano-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazol-5-yl]amino}-4-oxobutanoic Acid (*VI*)

A mixture of *III* (3.39 g; 0.01 mol) and succinic anhydride (*V*) (1 g; 0.01 mol) was fused by heating in an oil bath (140 °C) for 15 min at which time the melt resolidified. The resulting solid was allowed to reach room temperature, ground to a fine powder in mortar and stirred for 20 min in 1 M-sodium hydroxide solution (100 cm$^3$). The resulting suspension was filtered to remove insoluble material. The filtrate was acidified with dilute hydrochloric acid. The obtained solid was collected by filtration, washed with water, dried *in vacuo* and crystallized. Yield = 3.34 g

(76 %), m.p. = 263 °C (ethanol). For $C_{23}H_{17}N_7O_3$ ($M_r$ = 439.43) $w_i$(calc.): 62.87 % C, 3.90 % H, 22.31% N; $w_i$(found): 62.57 % C, 3.98 % H, 22.62 % N. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 3400—3100 $\nu$(NH and COOH), 2220 $\nu$(CN), 1675 $\nu$(CO), and 1655 $\nu$(CO). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 12.57 (s, 1H, COOH), 9.47 (s, 1H, NH), 7.61—7.34 (m, 11H, $H_{arom}$ and pyrazole C-3—H), 4.13 (t, 2H, $J$ = 12.5 Hz, $CH_2$), 3.86 (t, 2H, $J$ = 12.5 Hz, $CH_2$).

### Ethyl 3-[4-Oxo-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl]propionate (*VIII*)

Dry HCl gas was passed through a suspension of compound *VI* (13.2 g; 0.03 mol) in dry ethanol (200 cm$^3$) for 5 h. The system was protected from atmospheric moisture during this period with a calcium chloride tube. During the course of the reaction, the starting material was slowly dissolved and a new crystalline solid separated. The reaction mixture was finally heated under reflux for 30 min, cooled to 0 °C, and filtered. The collected solid was washed with dry ethanol to give 9.84 g (65 %) yield from the chloride salt of ethyl $\beta$-(pyrazolo[3,4-*d*]pyrimidinone)propionate *VII*. The free base *VIII* was liberated from its salt by dissolution in hot water (50 cm$^3$) followed by addition of sodium acetate to pH 8, filtration and washing with water and the product was crystallized. Yield = 3.53 g (74 %), m.p. = 235 °C (ethanol). For $C_{25}H_{21}N_7O_3$ ($M_r$ = 467.48) $w_i$(calc.): 64.23 % C, 4.53 % H, 20.97 % N; $w_i$(found): 64.34 % C, 4.29 % H, 20.65 % N. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 3150 $\nu$(NH), 1690 $\nu$(ester CO), 1665 $\nu$(CONH). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 8.25 (s, 1H, NH), 7.63—7.27 (m, 11H, $H_{arom}$ and pyrazole C-3—H), 4.33 (q, 2H, ester $CH_2$), 4.12 (t, 2H, $J$ = 12.3 Hz, $CH_2$), 3.24 (t, 2H, $J$ = 12.3 Hz, $CH_2$), 1.55 (t, 3H, ester $CH_3$).

### 3-[1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl]propanoic Acid (*IX*)

Compound *VIII* (4.67 g; 0.01 mol) was treated with sodium hydroxide solution (10 %, 25 cm$^3$) under reflux for 1 h. Acidification of the clear alkaline solution with dilute hydrochloric acid resulted in the separation of a solid which was collected by filtration, washed with ethanol and crystallized. Yield = 4.0 g (91 %), m.p. = 287 °C (dimethylformamide). For $C_{23}H_{17}N_7O_3$ ($M_r$ = 439.43) $w_i$(calc.): 62.87 % C, 3.91 % H, 22.31 % N; $w_i$(found): 62.60 % C, 3.76 % H, 22.28 % N. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 3490—3150 $\nu$(NH and COOH), 1655 $\nu$(CO). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 12.54 (s, 1H, COOH), 9.17 (s, 1H, NH), 7.63—7.39 (m, 11H, $H_{arom}$ and pyrazole C-3—H), 2.34 (t, 2H, $CH_2$), 1.66 (t, 2H, $CH_2$).

### 1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-7,8-dihydro-1*H*-pyrazolo[3,4-*d*]pyrrolo[1,2-*a*]pyrimidine-4,6-dione (*X*)

A suspension of *IX* (1.0 g) in toluene (50 cm$^3$) was boiled until approximately 10 cm$^3$ of the solvent had been removed (to remove any traces of moisture) and then acetic anhydride (10 cm$^3$) was added. The reaction mixture was then heated under reflux with stirring for 7 h. A calcium chloride tube was employed to protect the mixture against atmospheric moisture. The hot homogeneous solution was treated with charcoal and filtered while hot. The filtrate was cooled in an ice bath. The crystalline solid, which separated, was collected by filtration and washed with dry benzene. Yield = 0.8 g (81 %), m.p. = 175 °C (chloroform). For $C_{23}H_{15}N_7O_2$ ($M_r$ = 421.41) $w_i$(calc.): 65.55 % C, 3.58 % H, 23.27 % N; $w_i$(found): 65.80 % C, 3.47 % H, 23.58 % N. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 1655 $\nu$(CO), 1665 $\nu$(CO). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 7.67—7.21 (m, 11H, $H_{arom}$ and pyrazole C-3—H), 4.28 (t, 2H, $J$ = 7.6 Hz, $CH_2$), 3.11 (t, 2H, $J$ = 7.6 Hz, $CH_2$).

### 1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-6,7-dihydro-1*H*-pyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrimidine-4,8-dione (*XI*)

A suspension of *XII* (4.4 g; 0.01 mol) in glacial acetic acid (50 cm$^3$) containing 0.5 g of anhydrous sodium acetate was heated under reflux for 3 h. The reaction mixture was concentrated to dryness under reduced pressure and the residue was treated with dilute ammonium hydroxide. The formed precipitate was then recrystallized. Yield = 3.85 g (92 %), m.p. = 231 °C (toluene). For $C_{23}H_{15}N_7O_2$ ($M_r$= 421.41) $w_i$(calc.): 65.55 % C, 3.59 % H, 23.27 % N; $w_i$(found): 65.30 % C, 3.45 % H, 23.17 % N. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 1667 $\nu$(CO) and 1655 $\nu$(CO). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 7.44—7.19 (m, 10$H_{arom}$ and pyrazole C-3—H), 4.31 (t, 2H, $J$ = 8.5 Hz, $CH_2$), 3.32 (t, 2H, $J$ = 8.5 Hz, $CH_2$).

### 5-(2,5-Dioxopyrrolidin-1-yl)-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazole-4-carboxamide (*XII*)

Succinyl chloride (1.7 g; 0.011 mol) was added dropwise to a cold, stirred solution of *IV* (3.57 g; 0.01 mol) in 30 cm$^3$ of dry pyridine. The reaction mixture was left overnight at room temperature and then poured into 250 cm$^3$ of water and the solution was acidified with dilute hydrochloric acid. The solution was then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Yield = 3.16 g (72 %), m.p. = 212 °C (ethanol). For $C_{23}H_{17}N_7O_3$ ($M_r$ = 439.43) $w_i$(calc.): 62.87 % C, 3.90 % H, 22.31 % N; $w_i$(found): 62.71 % C, 3.53 % H,

22.64 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3385 $\nu$(CONH$_2$), 1658 $\nu$(CO), 1650 $\nu$(CO), 1645 $\nu$(CO). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 8.34 (s, 2H, CONH$_2$), 7.73—7.42 (m, 11H, H$_{arom}$ and pyrazole C-3—H), 4.21 (m, 4H, 2CH$_2$).

### 4-Chloro-*N*-[4-cyano-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazol-5-yl]butyramide (*XIII*)

4-Chlorobutyryl chloride (1.41 g; 0.011 mol) was added dropwise to a cooled, stirred solution of *III* (3.39 g; 0.01 mol) in dry pyridine (20 cm$^3$). The solution was left overnight at room temperature and then poured into water (200 cm$^3$) and acidified with dilute hydrochloric acid. The solution was then extracted with chloroform, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Yield = 4.35 g (90 %), m.p. = 191 °C (dioxan). For $C_{23}H_{18}ClN_7O$ ($M_r$ = 443.89) $w_i$(calc.): 62.23 % C, 4.09 % H, 7.99 % Cl, 22.09 % N; $w_i$(found): 62.55 % C, 3.89 % H, 7.75 % Cl, 22.12 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3328 $\nu$(NH), 2220 $\nu$(CN), and 1652 $\nu$(CO). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 8.13 (s, 1H, NH), 7.68 (s, 1H, pyrazole C-3—H), 7.48—7.23 (m, 11H, H$_{arom}$), 4.38 (t, 2H, CH$_2$), 3.17 (t, 2H, CH$_2$), 1.97 (m, 2H, CH$_2$). Mass spectrum, *m/z* ($I_r$/%): $M_r$ = 443.13 (100 %), "$M_r$ + 1" = 444.13 (25), and "$M_r$ + 2" = 445.12 (30).

### 1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-5-(2-oxopyrrolidin-1-yl)-1 *H*-pyrazole-4-carbonitrile (*XIV*)

A solution of sodium hydroxide (0.6 g; 0.015 mol) in water (10 cm$^3$) was added to a solution of compound *XIII* (4.4 g; 0.01 mol) in methanol (25 cm$^3$). The reaction mixture was allowed to stand at room temperature for 5 h, during which time a precipitate gradually separated, the mixture was then added to water (20 cm$^3$), extracted with three 20 cm$^3$ portions of chloroform. The combined extracts were washed with 1 M-hydrochloric acid (50 cm$^3$). The organic layer was dried over anhydrous magnesium sulfate and evaporated. Yield = 2.9 g (72 %), m.p. = 233 °C (ethanol). For $C_{23}H_{17}N_7O$ ($M_r$ = 407.43) $w_i$(calc.): 67.80 % C, 4.21 % H, 24.06 % N; $w_i$(found): 67.54 % C, 3.99 % H, 24.22 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 2220 $\nu$(CN), 1700 $\nu$(CO). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 7.68—7.23 (m, 11H, H$_{arom}$ and pyrazole C-3—H), 4.41 (t, 2H, CH$_2$), 3.35 (t, 2H, CH$_2$), 2.25 (m, 2H, CH$_2$). Mass spectrum, *m/z* ($I_r$/%): $M_r$ = 407.15 (100 %).

### 1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-7,8-dihydro-1*H*-pyrazolo[3,4-*e*]pyrrolo[1,2-*a*]pyrimidin-4(5*H*)-one (*XV*)

Dry hydrogen chloride gas was passed for a period of 3 h at room temperature through a suspension of *XIV* (4.07 g; 0.01 mol) in absolute ethanol (50 cm$^3$). The solution became warm and yellow solid separated. The reaction mixture was cooled and filtered. The collected solid was dissolved in water (25 cm$^3$), this solution was neutralized with sodium acetate and then extracted with chloroform. The extract was dried over anhydrous sodium sulfate and the solvent was evaporated. Yield = 3.7 g (91 %), m.p. = 196 °C (toluene). For $C_{23}H_{17}N_7O$ ($M_r$ = 407.43) $w_i$(calc.): 67.80 % C, 4.20 % H, 24.06 % N; $w_i$(found): 67.61 % C, 4.12 % H, 24.33 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3210 $\nu$(CONH), 2220 $\nu$(CN), 1685 $\nu$(CO). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 8.12 (s, 1H, NH), 7.68—7.57 (m, 11H, H$_{arom}$ and H-3), 4.62 (t, 1H, CH), 3.12 (t, 2H, CH$_2$), 2.88 (m, 2H, CH$_2$). Mass spectrum, *m/z* ($I_r$/%): $M_r$ = 407.13 (100 %).

### 1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (*XVI*)

A mixture of formic acid and formamide ($\varphi_r$ = 1 : 1.1) was added to *III* (3.4 g; 0.01 mol) in dimethylformamide (15 cm$^3$). The reaction mixture was heated for 10 h, the solvent was evaporated under reduced pressure and the precipitated product was filtered and recrystallized, brown crystals. Yield = 0.4 g (53 %), m.p. = 277 °C (ethanol). For $C_{20}H_{13}N_7O$ ($M_r$ = 367.36) $w_i$(calc.): 65.39 % C, 3.57 % H, 26.69 % N; $w_i$(found): 65.50 % C, 3.74 % H, 26.8 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3190 $\nu$(NH), 1680 $\nu$(CO).$^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 9.94 (br s, 1H, NH), 7.82—7.24 (m, 12H, H$_{arom}$, H-3 and H-6). Mass spectrum, *m/z* ($I_r$/%): $M_r$ = 367.14 (100 %).

### 1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (*XVII*)

A suspension of compound *III* (3.4 g; 0.01 mol) in formamide (15 cm$^3$) was heated under reflux for 2 h. The precipitated product which formed after cooling was filtered off and recrystallized, pale yellow crystals. Yield = 2.24 g (61 %), m.p. = 282 °C (acetic acid). For $C_{20}H_{14}N_8$ ($M_r$ = 366.38) $w_i$(calc.): 65.56 % C, 3.85 % H, 30.58 % N; $w_i$(found): 65.42 % C, 3.61 % H, 30.27 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3500—3330 $\nu$(NH$_2$). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 8.31—7.32 (m, 12H, H$_{arom}$, H-3 and H-6), 5.24 (s, 2H, NH$_2$). Mass spectrum, *m/z* ($I_r$/%): $M_r$ = 366.18 (100 %).

### Reaction of Compound *III* with Active Methylene Reagents

Titanium(IV) chloride (5.69 g; 0.03 mol) was added under stirring to an ice-cooled solution of compound *III* (3.390 g; 0.01 mol) and the active methylene compound (0.01 mol: malononitrile 0.66 g, ethyl cyanoacetate 1.13 g, or ethyl acetoacetate 1.30 g) in 1,2-

dichloroethane (25 $cm^3$). The reaction mixture was refluxed for 2 h, then saturated aqueous $Na_2CO_3$ solution (25 $cm^3$) and anhydrous $Na_2CO_3$ (10 g) were successively added. The reaction mixture was stirred and cooled in ice bath. The formed solid was removed by filtration and washed with hot $CHCl_3$. The combined filtrates were concentrated and the residue crystallized from the proper solvent to give the corresponding *XVIII*, *XIX*, and *XX*, respectively.

*4,6-Diamino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (XVIII).* Deep brown crystals. Yield = 2.4 g (60 %), m.p. = 220 °C (ethanol). For $C_{22}H_{15}N_9$ ($M_r$ = 405.41) $w_i$(calc.): 65.18 % C, 3.73 % H, 31.09 % N; $w_i$(found): 65.39 % C, 3.58 % H, 31.23 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3500—3280 $\nu$($NH_2$), 2220 $\nu$(CN). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 7.75—7.21 (m, 11H, $H_{arom}$ and H-3), 6.13 (s, 4H, $2NH_2$). Mass spectrum, *m/z* ($I_r$/%): $M_r$ = 405.15 (100 %).

*Ethyl 4,6-Diamino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (XIX).* Brown crystals. Yield = 3.17 g (70 %), m.p. over 300 °C (ethanol—DMF, $\varphi_r$ = 5 : 1). For $C_{24}H_{20}N_8O_2$ ($M_r$ = 452.47) $w_i$(calc.): 63.71 % C, 4.46 % H, 24.76 % N; $w_i$(found): 63.57 % C, 3.38 % H, 24.61 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3450—3150 $\nu$($NH_2$), 1680 $\nu$(ester CO). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 7.65—7.19 (m, 11H, $H_{arom}$ and H-3), 6.25 (br s, 2H, 4-$NH_2$ or 6-$NH_2$), 5.82 (br s, 2H, 4-$NH_2$ or 6-$NH_2$), 4.11 (q, $J$ = 7.5 Hz, 2H, ester $CH_2$), 1.17 (t, $J$ = 7.5 Hz, 3H, ester $CH_3$). Mass spectrum, *m/z* ($I_r$/%): 452.13 (100 %).

*Ethyl 4-Amino-6-methyl-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (XX).* Brown crystals. Yield = 2.9 g (64 %), m.p. = 235 °C (ethanol). For $C_{25}H_{21}N_7O_2$ ($M_r$ = 451.50) $w_i$(calc.): 66.5 % C, 4.69 % H, 21.72 % N; $w_i$(found): 66.87 % C, 4.49 % H, 24.85 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3440—3235 $\nu$($NH_2$), 1675 $\nu$(ester CO). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 7.60—7.22 (m, 11H, $H_{arom}$ and H-3), 5.74 (s, 2H, $NH_2$), 4.14 (q, $J$ = 7 Hz, 2H, ester $CH_2$), 2.65 (s, 3H, $CH_3$), 1.22 (t, $J$ = 7 Hz, H, ester $CH_3$). Mass spectrum, *m/z* ($I_r$/%): $M_r$ = 451.11 (100 %).

### 4-Amino-6-methyl-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (*XXI*)

A suspension of compound *XX* (4.51 g; 0.01 mol) in ammonium hydroxide solution (25 $cm^3$) was stirred overnight at room temperature. Then, the reaction mixture was neutralized with dilute hydrochloric acid to yield a white precipitate which was isolated by filtration and crystallized. Yield = 2.7 g (65 %), m.p. = 200 °C (ethanol). For $C_{23}H_{18}N_8O$ ($M_r$ = 422.44) $w_i$(calc.): 65.39 % C, 4.29 % H, 26.53 % N; $w_i$(found): 65.54 % C, 4.47 % H, 26.41 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3430—3150 $\nu$($NH_2$ and $CONH_2$), 1655 $\nu$(CO). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 8.95 (br s, 2H, $CONH_2$), 7.56—7.18 (m, 11H, $H_{arom}$ and H-3), 5.76 (br s, 2H, $NH_2$), 2.58 (s, 3H, $CH_3$). Mass spectrum, *m/z* ($I_r$/%): $M_r$ = 422.10 (100 %).

### 4-Amino-6-methyl-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (*XXII*)

A mixture of compound *XXI* (4.22 g; 0.01 mol) and $P_2O_5$ (20 g) was fused for 1 h. The reaction mixture was distilled under reduced pressure (by naked flame), product was isolated by condensation of the vapours over cold surface as crystalline needles. Yield = 2.00 (50 %), m.p. = 123 °C. For $C_{23}H_{16}N_8$ ($M_r$ = 404.43) $w_i$(calc.): 68.31 % C, 3.99 % H, 27.71 % N; $w_i$(found): 68.62 % C, 4.87 % H, 27.95 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3350—3330 $\nu$($NH_2$), 2216 $\nu$(CN). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 7.69—7.18 (m, 11H, $H_{arom}$ and H-3), 5.83 (br s, 2H, $NH_2$), 2.61 (s, 3H, $CH_3$). Mass spectrum, *m/z* ($I_r$/%): $M_r$ = 404.18 (100 %).

### 1-(5,6-Diphenyl[1,2,4]triazin-3-yl)-1*H*-pyrazolo[3,4-*b*]thieno[3,4-*e*]pyridine-4,5-diamine (*XXIII*)

Equimolar amounts of *XXII* (4.04 g; 0.01 mol) and elemental sulfur (0.32 g; 0.01 mol) in ethanol (50 $cm^3$) were treated with few drops of piperidine. The reaction mixture was refluxed for 3 h. The solid product which formed was collected by filtration and crystallized. Yield = 3.4 g (78 %), m.p. = 263 °C (dioxane). For $C_{23}H_{16}N_8S$ ($M_r$ = 436.49) $w_i$(calc.): 63.29 % C, 3.69 % H, 25.67 % N, 7.35 % S; $w_i$(found): 63.19 % C, 3.52 % H, 25.81 % N, 7.58 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3446—3320 $\nu$($NH_2$). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 7.60—6.35 (m, 12H, $H_{arom}$, H-3 and H-7), 6.71 (s, 2H, $NH_2$), 5.62 (s, 2H, $NH_2$). Mass spectrum, *m/z* ($I_r$/%): $M_r$ = 436.16 (100 %).

### 4,5-Diamino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazolo[3,4-*b*]furo[3,4-*g*]quinoline-6,8-dione (*XXV*)

Equimolar amounts of *XXIII* (4.36 g; 0.01 mol) and maleic anhydride (0.98 g; 0.01 mol) were heated over melting point without solvent (oil bath) for 15 min. The resulting solid product was washed several times with water and crystallized. Yield = 3.1 g (62 %), m.p. = 246 °C (dioxane). For $C_{27}H_{16}N_8O_3$ ($M_r$ = 500.47) $w_i$(calc.): 64.79 % C, 3.22 % H, 22.39 % N; $w_i$(found): 64.58 % C, 3.10 % H, 22.61 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3488—3310 $\nu$($NH_2$), 1780—1720 $\nu$(C=O). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 10.12 (br

s, 2H, $NH_2$), 7.55—6.83 (m, 12H, $H_{arom}$, H-3 and H-9), 5.62 (br s, 2H, $NH_2$). Mass spectrum, $m/z$ ($I_r$/%): $M_r$ = 500.13 (100 %).

### Reaction of Compound *III* with Acetic Anhydride

Compound *III* (3.39 g; 0.01 mol) was heated under reflux in acetic anhydride (25 $cm^3$) for 5 h. The excess acetic anhydride was removed under reduced pressure. The reaction mixture was allowed to stand at room temperature, during which time a precipitate gradually separated and was collected by filtration and crystallized to give compound *XXVII*. The filtrate was then added to water (20 $cm^3$) and the solid product that formed was filtered off and crystallized to give *XXVI*.

*1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-6-methyl-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one (XXVI).* Yellow crystals. Yield = 2.3 g (60.2 %), m.p. = 123 °C (ethanol). For $C_{21}H_{15}N_7O$ ($M_r$ = 381.39) $w_i$(calc.): 66.13 % C, 3.96 % H, 25.71 % N; $w_i$(found): 65.99 % C, 3.68 % H, 25.43 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3180 $\nu$(NH), 1680 $\nu$(CO). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 9.36 (s, 1H, NH), 7.75—7.21 (m, 11H, $H_{arom}$ and H-3), 2.42 (s, 3H, $CH_3$). Mass spectrum, $m/z$ ($I_r$/%): $M_r$ = 381.10 (100 %).

*5,5-Diacetylamino-1-(5,6-diphenyl)-1,2,4-triazinopyrazole-4-carbonitrile (XXVII).* Deep brown crystals. Yield = 0.35 g (8.3 %), m.p. = 215 °C (dioxane). For $C_{23}H_{17}N_7O_2$ ($M_r$ = 423.43) $w_i$(calc.): 65.24 % C, 4.05 % H, 23.16 % N; $w_i$(found): 66.34 % C, 4.27 % H, 22.81 % N. IR spectrum, $\tilde{\nu}/cm^{-1}$: 2220 $\nu$(CN), 1663, 1660 $\nu$(2NCO$CH_3$). $^1$H NMR spectrum (DMSO-$d_6$), $\delta$: 7.63—7.20 (m, 11H, $H_{arom}$ and H-3), 3.17 (s, 6H, N($COCH_3$)$_2$). Mass spectrum, $m/z$ ($I_r$/%): $M_r$ = 423.18 (100 %).

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