Synthesis of Various Pyrazolo[4′,3′:5,6]pyrano[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines and Pyrazolo[4″,3″:5′,6′]pyrano[2′,3′:4,5]pyrimido[1,6-*b*][1,2,4]triazines

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A number of heterocyclic compounds **5–13** were prepared by the reaction of 6-amino-1,4,5,6-tetrahydro-5-imino-3-methyl-1,4-diphenylpyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine (**3**) with ethyl 2-cyano-3-ethoxy-2-propenoate, ethoxymethylenemalononitrile, ethyl cyanoacetate, malononitrile, ethyl pyruvate, oxalyl chloride, ethyl chloroformate, and 3-methyl-4-nitroso-1-phenylpyrazol-5(4*H*)-one, respectively.

Several pyrano[2,3-*c*]pyrazoles are reported to have useful biological effects, such as analgesic and antiinflammatory activities.[1] The biological activity of fused azoles has led to intensive research on their synthesis.[2–6]

Triazolopyrimidines, and particularly triazolo[1,5-*c*]-pyrimidines, show some of the useful pharmacological properties of theophylline to a greater degree.[7,8] The latter were shown to protect guinea pigs against the toxic effects of inhaled histamine spray.[7,8]

We report here on the synthesis of pyrazolo[4′,3′:5,6]pyrano[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine and pyrazolo[4″,3″:5′,6′]pyrano[2′,3′:4,5]pyrimido[1,6-*b*]-[1,2,4]triazine derivatives via reaction of 6-amino-1,4,5,6-tetrahydro-5-imino-3-methyl-1,4-diphenylpyrazolo[4′,3′:5,6]pyrano-[2,3-*d*]pyrimidine (**3**) with different reagents. Compound **3** was prepared by treating ethyl *N*-(5-cyano-1,4-dihydro-3-methyl-1,4-diphenylpyrano-[2,3-*c*]pyrazol-6-yl)methanimidate (**2**) with hydrazine hydrate.[9,10] On the other hand compound **2** was prepared by the reaction of 6-amino-5-cyano-1,4-dihydro-3-methyl-1,4-diphenylpyrano[2,3-*c*]pyrazole (**1**)[11,12] with an equimolar amount of triethyl orthoformate and acetic anhydride.[9,10](Scheme **A**, Table).

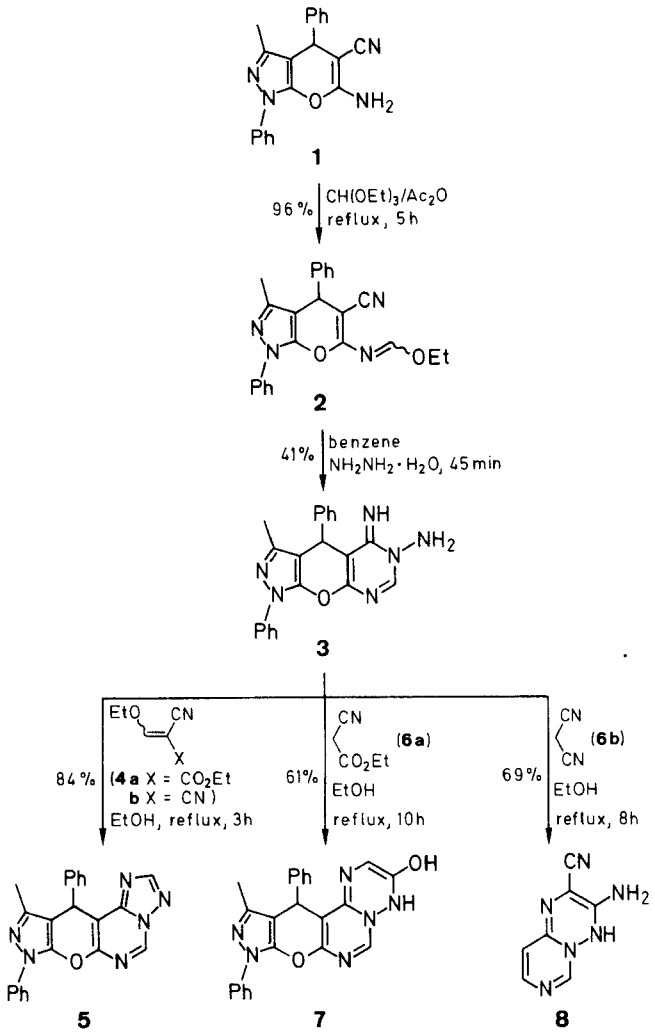
Compound **3** reacted with ethyl 2-cyano-3-ethoxy-2-propenoate (**4a**) or ethoxymethylenemalononitrile (**4b**) to give the same product, 8,11-dihydro-10-methyl-8,11-diphenylpyrazolo[4′,3′:5,6]pyrano[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (**5**), based on the absence of NH and NH_2 absorptions in the IR spectrum (Scheme **A**, Table).

The activity of **3** toward active methylenes was also tested. Thus, with ethyl cyanoacetate (**6a**), 9,12-dihydro-3-hydroxy-11-methyl-9,12-diphenyl-2*H*-pyrazolo[4″,3″:5′,6′]pyrano[2′,3′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (**7**) was the reaction product as confirmed by its IR spectrum, which indicates an absorption band at ν = 3400 cm^{-1} corresponding to NH and OH groups, as well as by its ^{1}H-NMR spectra and elemental analyses. 3-Amino-2-cyanopyrimido[1,6-*b*][1,2,4]triazine (**8**) was obtained from the reaction of **3** with malononitrile (**6b**).

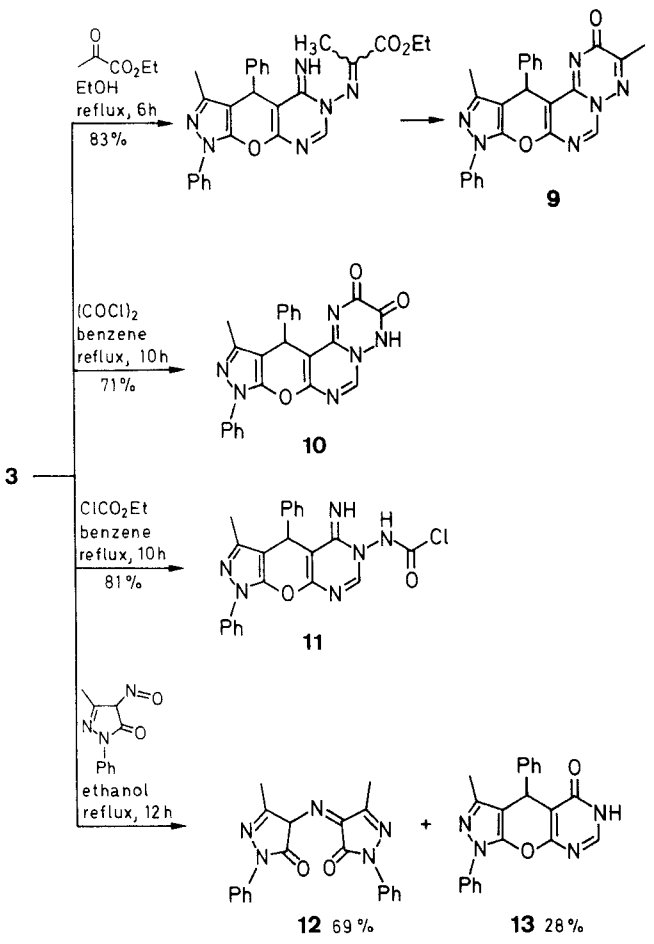
Condensation of ethyl pyruvate with **3** in absolute ethanol led to the cyclized product **9**, whose structure was confirmed by elemental analyses and by the presence of an amide carbonyl band in the IR spectrum at ν = 1680 cm^{-1}, and ^{1}H-NMR data (Table).

Reaction of **3** with oxalyl chloride furnished via cyclization,[13] 9,12-dihydro-11-methyl-9,12-diphenyl-2*H*-pyrazolo[4″,3″:5′,6′]pyrano[2′,3′:4,5]pyrimido[1,6-*b*]-[1,2,4]triazine-2,3(4*H*)-dione (**10**), while ethyl chloroformate reacted with **3** to give 6-chlorocarbonylamino-1,4,5,6-tetrahydro-5-imino-3-methyl-1,4-diphenylpyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine (**11**) (Scheme **B**, Table).

Refluxing compound **3** with 3-methyl-4-nitroso-1-phenylpyrazol-5(4*H*)-one in absolute ethanol afforded two products. One of them was identified as rubazonic acid



Scheme A



Scheme B

(12)[14] by its melting point and mixed melting point with an authentic sample,[14] and the other product isolated from the filtrate was identified as 1,4-dihydro-3-methyl-1,4-diphenylpyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidin-5(6*H*)-one (**13**) (Scheme **B**, Table).

In summary, we have found access to several interesting heterocyclic compounds, which may have biological activities, by utilizing simple reaction sequences starting from the heterocycle **3**.

Melting points are uncorrected. The microanalyses were performed by the microanalysis unit at Assiut University. IR spectra were recorded as KBr discs using a Pye-Unicam SP-1100 spectrophotometer ^{1}H-NMR spectra were recorded on a Varian A-60 spectrometer. Compound **1** was prepared according to literature.[11,12]

Ethyl *N*-(5-Cyano-1,4-dihydro-3-methyl-1,4-diphenylpyrano[2,3-*c*]-pyrazol-6-yl)methanimidate (2):
A mixture of **1** (1.64 g, 0.005 mol), triethyl orthoformate (0.741 g, 0.005 mol) and acetic anhydride (16 mL) is refluxed for 5 h. The solvent is removed under reduced pressure and the resulting solid product is crystallized from benzene to give colourless needles; yield: 1.85 g (96%).

6-Amino-1,4,5,6-tetrahydro-5-imino-3-methyl-1,4-diphenylpyrazolo-[4′,3′:5,6]-pyrano[2,3-*d*]pyrimidine (3):
To a solution of **2** (1.15 g, 0.003 mol) in benzene (20 mL) is added a solution of hydrazine hydrate (5 mL) in H_2O (10 mL) and the mixture is stirred for 45 min. Then it is allowed to stand overnight, the precipitate formed is filtered, dried and crystallized from benzene to furnish colourless flakes; yield 0.45 g (41%).

8,11-Dihydro-10-methyl-8,11-diphenylpyrazolo[4′,3′:5,6]pyrano-[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5):
To a solution of **3** (0.37 g, 0.001 mol) in absolute EtOH (100 mL) is added ethyl 2-cyano-3-ethoxy-2-propenoate (**4a**) or ethoxymethylenemalononitrile (**4b**; 0.001 mol) and the mixture is refluxed for 3 h. On cooling, a solid product separates, which is collected, and crystallized from benzene to afford white needles; yield: 0.32 g (84%).

9,12-Dihydro-3-hydroxy-11-methyl-9,12-diphenyl-2*H*-pyrazolo-[4″,3″:5′,6′]pyrano[2′,3′:4,5]pyrimido[1,6-*b*][1,2,4]triazine (7):
A mixture of **3** (0.37 g, 0.001 mol) and ethyl cyanoacetate (0.1 mL, 0.001 mol) in absolute EtOH (100 mL) is refluxed for 10 h. After cooling, the precipitated product is collected and crystallized from EtOH to give pale yellow flakes; yield: 0.25 g (61%).

3-Amino-2-cyanopyrimido[1,6-*b*][1,2,4]triazine (8):
A solution of **3** (0.37 g, 0.001 mol) in absolute EtOH (100 mL) is refluxed with malononitrile (0.066 g, 0.001 mg) for 8 h. The mixture is cooled and the solid product is collected by filtration and crystallized from EtOH to afford pale yellow needles; yield: 0.12 g (69%).

9,12-Dihydro-3,11-dimethyl-9,12-diphenyl-2*H*-pyrazolo[4″,3″:5′,6′]-pyrano[2′,3′:4,5]pyrimido[1,6-*b*][1,2,4]triazin-2-one (9):
To a solution of **3** (0.37 g, 0.001 mol) in absolute EtOH (100 mL) is added ethyl pyruvate (0.11 mL, 0.001 mol) and the mixture is refluxed for 6 h. After cooling, the precipitated product is collected and crystallized from EtOH to give pale yellow needles; yield: 0.35 g (83%).

Table. Compounds **2**–**13** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	IR (KBr) ν (cm^{-1})	UV[b] λ_{max} (nm) (log ε)	^{1}H-NMR[c] δ, J(Hz)
2	96	128	$C_{23}H_{20}N_4O_2$ (384.4)	2240 (C≡N)	255 (4.34)	1.40 (t, 3H, J = 6, CH_3), 1.90 (s, 3H, CH_3), 4.38 (q, 2H, J = 6, CH_2), 4.75 (s, 1H, H-4), 7.45 (m, 10H_{arom}), 8.20 (s, 1H, CHOEt)
3[d]	41	208–209	$C_{21}H_{18}N_6O$ (370.4)	3380, 3340 (NH_2), 3100 (NH)	246 (4.20), 214 (4.18)	1.95 (s, 3H, CH_3), 5.00 (s, 1H, H-4)[15], 5.45 (s, 1H, NH), 7.55 (m, 10H_{arom}), 8.21 (s, 1H, H-7)[16]
5[d]	84	267–268	$C_{22}H_{16}N_6O$ (380.4)	–	372 (4.0)	2.05 (s, 3H, CH_3), 5.65 (s, 1H, H-11), 7.58 (m, 10H_{arom}), 8.30 (s, 1H, H-2), 9.20 (s, 1H, H-5)
7	61	275	$C_{23}H_{18}N_6O_2$ (410.4)	3400 (br, NH, OH)	255 (4.40)	1.93 (s, 3H, CH_3), 4.30 (s, 1H, NH), 5.61 (s, 1H, H-12), 7.43 (m, 10H_{arom}), 8.50 (1H, H-2), 9.60 (s, 1H, H-6)
8	69	338–340	$C_7H_6N_6$ (174.2)	3440–3400 (NH_2), 3350 (NH), 2200 (C≡N)	338 (4.36)	5.85 (s, 1H, NH), 5.95 (s, 1H, H-9), 7.60 (s, 1H, H-8), 8.00 (s, 1H, H-6)
9[d]	83	287	$C_{24}H_{18}N_6O_2$ (422.5)	1680 (C=O)	260 (4.46), 232 (4.48), 222 (4.43)	2.03 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.53 (s, 1H, H-12), 7.45 (m, 10H_{arom}), 8.53 (s, 1H, H-6)
10	71	341	$C_{23}H_{16}N_6O_3$ (424.4)	3450 (br, NH), 1710 (C=O)	–	2.00 (s, 3H, CH_3), 4.50 (s, 1H, NH), 5.43 (s, 1H, H-12), 7.48 (m, 10H_{arom}), 8.93 (s, 1H, H-6)
11	81	222–224	$C_{22}H_{16}ClN_6O_2$ (431.9)	3500–3140 (br, NH), 1670 (C=O)	244 (4.29)	1.95 (s, 3H, CH_3), 5.53 (s, 1H, H-4), 6.65 (s, 2H, NH_2), 7.30 (m, 10H_{arom}), 8.73 (s, 1H, H-7)
12	69	182	181–182[14]	1720 (C=O)	–	–
13	28	123–125	$C_{21}H_{16}N_4O_2$ (356.4)	3070 (NH), 1720 (C=O)	–	2.30 (s, 3H, CH_3), 4.15 (d, 1H, J = 6, NH), 5.61 (s, 1H, H-4), 7.55 (m, 10H_{arom}), 8.20 (s, 1H, H-7)

[a] Satisfactory microanalyses obtained: C ±0.42, H ±0.27, N ±0.36 (exception: **10**, N −0.44).
[b] Solvent: DMF for **5**, **8**; MeOH for **2**, **3**, **7**, **9**, **11**.
[c] Solvent: $CDCl_3$ for **2**, **3**, **5**, **9**, **11**, **13**; DMSO-d_6 for **7**, **8**, **10**.
[d] MS: m/z = 370 (M^+), 380 (M^+), 422 (M^+), for compounds **3**, **5** and **9**, respectively.

9,12-Dihydro-11-methyl-9,12-diphenyl-2*H*-pyrazolo[4″,3″:5′,6′]pyrano[2′,3′:4,5]pyrimido[1,6-*b*][1,2,4]triazine-2,3(4*H*)-dione (10):
A mixture of **3** (0.37 g, 0.001 mol) and oxalyl chloride (0.12 mL) in dry benzene (100 mL) is refluxed for 10 h. After cooling, the product is collected and crystallized from AcOH to give yellow needles, yield: 0.3 g (71%).

6-Chlorocarbonylamino-1,4,5,6-tetrahydro-5-imino-3-methyl-1,4-diphenylpyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine (11):
To a solution of **3** (0.37 g, 0.001 mol) in dry benzene (100 mL) is added an excess of ethyl chloroformate (0.5 mL) and refluxed for 10 h. After cooling, the solid product formed is collected and crystallized from benzene/EtOH (3:1) to furnish white flakes, yield: 0.35 g (81%).

Rubazonic Acid (12) and 1,4-Dihydro-3-methyl-1,4-diphenylpyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidin-5(6*H*)-one (13):
A solution of **3** (0.37 g, 0.001 mol) in absolute EtOH (100 mL) is refluxed with 3-methyl-4-nitroso-1-phenylpyrazol-5(4*H*)-one for 12 h. The color of the mixture becomes deep red and a red precipitate slowly separates out while hot. After cooling, the precipitate is collected and crystallized from petroleum ether (bp 40–60°C) to give deep red needles of rubazonic acid **(12)**; yield: 0.25 g (69%).

The filtrate is concentrated under reduced pressure, and the solid obtained is filtered and washed with petroleum ether (bp 60–80°C) to afford **13**, which is crystallized from petroleum ether (bp 60–80°C) to give orange crystals; yield: 0.1 g (28%).

The authors thank Dr. Kurt L. Loening, the Nomenclature Director of the Chemical Abstracts Service for naming some of the products reported in this paper.

Received: 10 December 1989; revised: 8 March 1990

(1) Kuo, S.C.; Huang, L.J.; Nakamura, H. *J. Med. Chem.* **1984**, *27*, 539.
(2) Hori, H.; Ito, E.; Jakta, T.; Koyama, G.; Umezawa, H. *J. Antibiot.* **1964**, *17 A*, 96.
(3) Koyama, G.; Umezawa, H. *J. Antibiot.* **1965**, *18 A*, 175.
(4) Robins, R.K.; Beaman, A.G. *J. Heterocycl. Chem.* **1963**, *3*, 110.
(5) Elnagdi, M.H.; Wamhoff, H. *Chem. Lett.* **1981**, 419.
(6) Elnagdi, M.H.; Wamhof, H. *J. Heterocycl. Chem.* **1981**, *18*, 1987.
(7) Miller, G.W.; Rose, F.L. *J. Chem. Soc.* **1963**, 5642.
(8) Miller, G.W.; Rose, F.L. *J. Chem. Soc.* **1965**, 3357.
(9) Taylor, E.C.; Loeffler, P.K. *J. Am. Chem. Soc.* **1960**, *82*, 3147.
(10) Sangapoure, S.S.; Agasimundin, Y.S. *Indian. J. Chem.* **1980**, *19 B*, 115.
(11) Tacconi, G.; Gatti, G.; Desimoni, G. *J. Prakt. Chem.* **1980**, 322, 831.
(12) Sharanina, L.G.; Promonenkov, V.K.; Marshtupa, V.P.; Pashchenko, A.V.; Puzanova, V.V.; Sharanin, Yu.A.; Klyuev, N.A.; Gusev, L.F.; Gnatusina, A.P. *Khim. Geterotsikl. Soedin* **1982**, 801; *C.A.* **1982**, *97*, 10991.
(13) Steglich, W.; Schmidt, H.; Hollitzer, O. *Synthesis* **1978**, 622.
(14) Metwally, M.A.; Younes, M.I.; Metwally, S.A.; El-Zohry, M.F. *Indian J. Chem.* **1985**, *24 B*, 870.
(15) Mityurina, K.V.; Kharchenko, V.G.; Cherkesova, L.V. *Khim. Geterotsikl. Soedin.* **1982**, 317; *C.A.* **1982**, *96*, 217757.
(16) Rousseaux, O.; Blondeau, D.; Sliwa, H. *Tetrahedron Lett* **1986**, *27*, 3127.