Misbahul Ain Khan* [a,b], Gwynn Pennant Ellis [c] and Mario Celso Pagotto [b,d]

[a] Laboratorio de Quimica Medicinal, Faculdade de Farmacia,
Universidade Federal Fluminense, Santa Rosa, Niteroi, RJ, 24230-000, Brasil
[b] Secao de Quimica, Instituto Militar de Engenharia, Praia Vermelha, Rio de Janeiro, RJ, Brasil
[c] Department of Chemistry, University of Wales Institute of Science and Technology, Cardiff, Wales, UK
[d] Liquid Quimica, Estrada Sr. Rene Fonseca, s/n, Cubatao, SP, 11573-904, Brasil
Received July 10, 1999

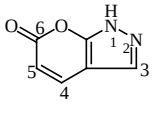
Various derivatives of title ring system were synthesized by Claisen condensation of 4 acetyl-5-hydroxypyrazoles with appropriate esters, followed by acid-catalyzed ring closure.

J. Heterocyclic Chem., **38**, 193 (2001).

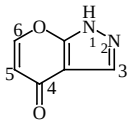
Replacement of the benzene ring in coumarin and chromone by a pyrazole ring can lead to the heterocyclic isosteric systems 1*H*-pyrano[2,3-*c*]pyrazol-6-one (**1**) and 1*H*-pyrano[2,3-*c*]pyrazol-4-one (**2**) respectively. While **1** has been mentioned in the literature and various of its derivatives and their reactions have been described [1], not much is known about **2** except a few attempts at the synthesis of this system as reported by Heinish *et al*., and Gelin *et al*. [2]. Previously, we communicated the synthesis of this system (**2**) [3] and now would like to report in detail the synthesis of various derivatives of (**2**).

The starting material, pyrazolones (**3-6**), were prepared according to literature methods [4-7] by reaction of the appropriate hydrazines with β-ketoesters. These pyrazolones when heated with acetic anhydride and sodium acetate [8] furnished the respective 4-acetyl-5-hydroxypyrazoles (**7-10**). The infrared and ^{1}H-nmr spectra support the tuatomeric "4-acetyl-5-hydroxypyrazoles" structures. The infrared spectra displayed a strong hydrogen-bonded carbonyl absorption in the region 1640-1620 cm^{-1} and a weak and broad hydroxyl absorption between 3270-3100 cm^{-1}. In the ^{1}H-nmr spectra one proton singlet in a low magnetic field (δ 10.30-12.85) was observed for **7-9** which could be ascribed to the hydroxyl proton. For **10**, however, this proton was observed at δ 7.05.

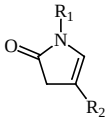
A Claisen condensation of these hydroxypyrazoles with the appropriate esters in the presence of base (sodium ethoxide for diethyl oxalate and sodium hydride



1

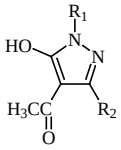


2



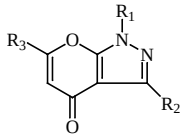
3-6

3 $R_1 = C_6H_5$; $R_2 = CH_3$
4 $R_1 = CH_3$; $R_2 = C_6H_5$
5 $R_1 = R_2 = C_6H_5$
6 $R_1 = R_2 = CH_3$



7-10

7 $R_1 = C_6H_5$; $R_2 = CH_3$
8 $R_1 = CH_3$; $R_2 = C_6H_5$
9 $R_1 = R_2 = C_6H_5$
10 $R_1 = R_2 = CH_3$



11-28

11 $R_1 = C_6H_5$; $R_2 = CH_3$; $R_3 = CO_2C_2H_5$
12 $R_1 = CH_3$; $R_2 = C_6H_5$; $R_3 = CO_2C_2H_5$
13 $R_1 = C_6H_5$; $R_2 = R_3 = CH_3$
14 $R_1 = R_3 = CH_3$; $R_2 = C_6H_5$
15 $R_1 = R_3 = C_6H_5$; $R_2 = CH_3$
16 $R_1 = CH_3$; $R_2 = R_3 = C_6H_5$
17 $R_1 = R_2 = C_6H_5$; R_3 = 2-furyl
18 $R_1 = C_6H_5$; $R_2 = CH_3$; R_3-2-furyl
19 $R_1 = CH_3$; $R_2 = C_6H_5$; R_3 = 2-furyl
20 $R_1 = R_2 = C_6H_5$; R_3 = 3-pyridyl
21 $R_1 = C_6H_5$; $R_2 = CH_3$; R_3 = 3-pyridyl
22 $R_1 = CH_3$; $R_2 = C_6H_5$; R_3 = 3-pyridyl
23 $R_1 = C_6H_5$; $R_2 = CH_3$; $R_3 = CO_2H$
24 $R_1 = CH_3$; $R_2 = C_6H_5$; $R_3 = CO_2H$
25 $R_1 = R_2 = CH_3$; $R_3 = CO_2H$
26 $R_1 = C_6H_5$; $R_2 = CH_3$; $R_3 = CONH_2$
27 $R_1 = C_6H_5$; $R_2 = CH_3$; $R_3 = CN$
28 $R_1 = C_6H_5$; $R_2 = CH_3$; R_3 = 5-tetrazolyl

Table 1

Data for 1*H*-pyrano[2,3-*c*]pyrazol-4-ones

Compound No.	Yield (%)	mp °C (from aqueous ethanol)	Molecular Formula	IR (cm^{-1})	^{1}H-nmr δ/ppm (J in Hz) (solvent)
11	74	127-128	$C_{16}H_{14}N_2O_4$	1738 (C=O ester) 1655 (C=O Pyrone) 1135 (C-O-C-Pyrone) 870 (C-H Pyrone)	1.40 (3H, t, J = 8, O-CH_2-CH_3); 2.60 (3H, t, CH_3); 4.40 (2H, q, O-CH_2-CH_3, J = 8), 7.00 (1H, s, H-5); 7.62 (5H, m,Phenyl-H) (deuteriochloroform)
12	86	184-185	$C_{16}H_{14}N_2O_4$	1735 (C=O ester) 1658 (C=O Pyrone) 1135 (C-O-C Pyrone) 875 (C-H Pyrone)	1.42 (3H, t, J = 8, O-CH_2-CH_3); 4.42 (2H, q, J = 8, O-CH_2-CH_3); 3.95 (3H, s, CH_3); 7.00 (1H, s, H-5) 7.40-8.28 (5H, m, Phenyl-H) (deuteriochloroform)
13	20	152-153	$C_{14}H_{12}N_2O_2$	1660 (C=O Pyrone) 1168 (C-O-C Pyrone) 930 (C-H Pyrone)	2.38 (3H, s, CH_3-6); 2.60(3H, s, CH_3-3); 5.98 (1H, s, H-5); 7.47 (5H, m, ph-H) (deuteriochloroform)
14	10	187-188	$C_{14}H_{12}N_2O_2$	1665 (C=O Pyrone) 1170 (C-O-C Pyrone) 840 (C-H Pyrone)	2.35 (3H, s, CH_3-3); 3.85 (3H, s, N-CH_3); 6.02 (1H, s, H-5); 7.40-8.30 (5H, m, Phenyl H) (deuteriodimethyl sulfoxide)
15	50	210-211	$C_{19}H_{14}N_2O_2$	1665 (C=O Pyrone) 1105 (C-O-C Pyrone) 850 (C-H Pyrone)	2.63 (3H, s, CH_3); 6.64 (1H, s, H-5); 7.62 (10H, m, Phenyl H) (deuteriochloroform)
16	15	181-182	$C_{19}H_{14}N_2O_2$	1640 (C=O Pyrone) 1135 (C-O-C Pyrone) 840 (C-H Pyrone)	4.00 (3H, s, CH_3); 6.65 (1H, s, H-5); 7.60-8.30 (10H, m, Phenyl H) (deuteriochloroform)
17	37	219-220	$C_{22}H_{14}N_2O_3$	1648 (C=O Pyrone) 1130 (C-O-C Pyrone) 850 (C-H Pyrone)	6.50 (1H, m, furan H-4); 6.54 (1H, s, H-5); 6.90 (1H, d, J = 7, furan H-3) 7.60-8.40 (11H, m, Phenyl H and furan H-5) (deuteriochloroform)
18	27	201-202	$C_{17}H_{14}N_2O_3$	1660 (C=O Pyrone) 1095 (C-O-C Pyrone) 850 (C-H Pyrone)	2.65 (3H, s, CH_3); 6.58 (1H, s, H-4); 6.60 (1H, s, H-5); 7.00 (1H, d, J = 7, H-3); 7.66 (6H, m, Phenyl H and H-5) (deuteriochloroform)
19	37	202-203	$C_{17}H_{14}N_2O_3$	1655 (C=O Pyrone) 1125 (C-O-C Pyrone) 850 (C-H Pyrone)	3.90 (3H, s, CH_3); 6.42 (1H, s, H-5); 6.73 (1H, m, H-4); 7.94 (1H, d, J = 7, H-3); 7.66 (6H, m). (Phenyl-H and H-5) (deuteriodimethyl sulfoxide)
20	37	255-256	$C_{23}H_{15}N_3O_2$	1648 (C=O Pyrone) 1140 (C-O-C Pyrone) 880 (C-H Pyrone)	7.55-8.12 (11H, m, Phenyl H and H-5) 9.02 (4H, m, pyridine-H). (deuteriochloroform-trifluoro acetic acid)
21	32	207-208	$C_{18}H_{13}N_3O_2$	1660 (C=O Pyrone) 1110 (C-O-C Pyrone) 895 (C-H Pyrone)	2.52 (3H, s, CH_3); 6.98 (1H, s, H-5); 7.70 (5H, m, C_6H_5); 8.10-9.15(4H, m, pyridine-H) (deuteriodimethyl sulfoxide)
22	50	224-225	$C_{18}H_{13}N_3O_2$	1630 (C=O Pyrone) 1140 (C-O-C Pyrone) 880 (C-H Pyrone)	3.95 (3H, s, CH_3); 6.62 (1H, s, H-5); 7.30 (5H, m, C_6H_5); 8.10-9.10(4H, m, pyridine-H) (deuteriochloroform)

Table 1 (continued)

Compound No.	Yield (%)	mp °C (from) (aqueous ethanol)	Molecular Formula	IR (cm^{-1})	^{1}H-nmr δ/ppm (J in Hz) (solvent)
23	74	277-278	$C_{14}H_{10}N_2O_4$	3000-2500 (br-OH) 1720 (C=O acid) 1630 (C=O Pyrone) 1128 (C-O-C Pyrone) 860 (C-H Pyrone)	2.50 (3H, s, CH_3); 6.82 (1H, s, H-5); 7.65 (5H, m, C_6H_5); (deuteriochloroform-deuterio dimethyl sulfoxide)
24	69	> 300	$C_{14}H_{10}N_2O_4$	3000-2500 (br-OH) 1740 (C=O acid) 1635 (C=O Pyrone) 1150 (C-O-C Pyrone) 890 (C-H Pyrone)	4.18 (3H, s, CH_3); 7.50-7.87 (6H, m, Phenyl H and H-5) (deuteriodimethyl sulfoxide-trifluoro acetic acid
25	35	218-220	$C_9H_8N_2O_4$	3150-2500 (br-OH) 1705 (C=O acid) 1630 (C=O Pyrone) 1115 (C-O-C Pyrone) 895 (C-H Pyrone)	2.40 (3H, s, CH_3-3); 3.35 (3H, s, N-CH_3); 7.40 (1H, s, H-5). (deuteriodimethyl sulfoxide)
26	79	272-273	$C_{14}H_{11}N_3O_3$	3400 (NH) 1695 (C=O amide) 1660 (C=O Pyrone) 1115 (C-O-C Pyrone) 895 (C-H Pyrone)	2.52 (3H, s, CH_3); 7.80 (5H, m, C_6H_5); 6.85 (1H, s, H-5) (deuteriodimethyl sulfoxide)
27	91	150-151	$C_{14}H_9N_3O_2$	2230 (C≡N)[a] 1665 (C=O Pyrone) 1145 (C-O-C Pyrone) 850 (C-H Pyrone)	2.61 (3H, s, CH_3); 6.78 (1H, s, H-5); 7.60 (5H, m, C_6H_5). (deuteriochloroform)
28	87	267-268	$C_{14}H_{10}N_6O_2$	3070 (NH) 1655 (C=O Pyrone) 1125 (C-O-C Pyrone) 895 (C-H Pyrone)	2.58 (3H, s,); 7.05 (1H, s, H-5); 7.62 (5H, m, C_6H_5). Deutrio dimethyl sulfoxide - deuteriochloroform

[a] – in nujol

for other esters)provides an intermediate "β-diketone" which was cyclized in an acid solution to the respective 1*H*-pyrano[2-3-*c*]pyrazol-4-ones (**11-22**) [9], (Scheme). An intermediate-β-diketone from the reaction of **10** with diethyl oxalate on cyclization gave a mixture of the expected ester and the corresponding acid (**25**). This mixture, as well as the esters **11** and **12**, on acid hydrolysis afforded the "corresponding" acids **23-25**.

An ammonolysis [10] of ester **11** afforded the amide (**26**) in 79% yield. The amide (**26**) on dehydration with *p*-toluenesulfonyl chloride in pyridine [10] afforded the nitrile (**27**) which in turn, on reaction with sodium azide in *N*,*N*-dimethylformamide [11] gave 3-methyl-1-phenyl-6-(tetrazol-5-yl)-1*H*-pyrano[2,3-*c*]pyrazol-4-one (**28**) in 87% yield.

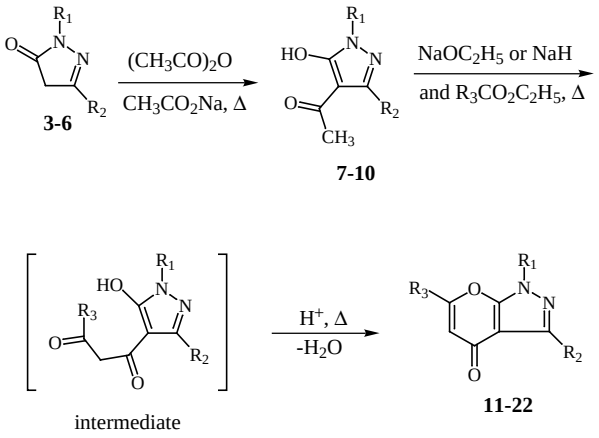
All the 1*H*-pyrano[2,3-*c*]pyrazol-4-ones (**11-28**) obtained during the present work are presented in Table 1 and were characterized by elemental analyses, infrared and ^{1}H-nmr spectra (Tables 1 and 2). The infrared spectra of new compounds **11-28** displayed the characteristic absorption band for the pyrone ring carbonyl in the region 1665-1630 cm^{-1}, the C-O-C

Table 2

Elemental Analyses for 1*H*-pyrano[2,3-*c*]pyrazol-4-ones

No.	Molecular Formula	Compound Calculated (%)			Found (%)		
		C	H	N	C	H	N
11	$C_{16}H_{14}N_2O_4$	64.42	4.73	9.39	64.31	4.80	9.45
12	$C_{16}H_{14}N_2O_4$	64.42	4.73	9.39	64.38	4.93	9.28
13	$C_{14}H_{12}N_2O_2$	69.99	5.03	11.66	70.08	4.94	11.66
14	$C_{14}H_{12}N_2O_2$	69.99	5.03	11.66	70.10	5.11	11.38
15	$C_{19}H_{14}N_2O_2$	75.48	4.67	9.27	75.13	4.77	9.33
16	$C_{19}H_{14}N_2O_2$	75.48	4.67	9.27	75.37	4.67	9.05
17	$C_{22}H_{14}N_2O_3$	74.57	3.98	7.91	74.31	3.86	7.64
18	$C_{17}H_{14}N_2O_3$	69.86	4.14	9.58	69.73	4.03	9.41
19	$C_{17}H_{14}N_2O_3$	69.86	4.14	9.58	69.95	4.01	9.35
20	$C_{23}H_{15}N_3O_2$	75.60	4.14	11.50	75.31	4.28	11.27
21	$C_{18}H_{13}N_3O_2$	71.26	4.32	13.85	71.02	4.30	13.68
22	$C_{18}H_{13}N_3O_2$	71.26	4.32	13.85	70.98	4.30	13.53
23	$C_{14}H_{10}N_2O_4$	62.22	3.73	10.37	61.92	3.74	10.27
24	$C_{14}H_{10}N_2O_4$	62.22	3.73	10.37	61.83	3.76	10.34
25	$C_9H_8N_2O_4$	51.93	3.87	13.47	51.71	3.65	13.37
26	$C_{14}H_{11}N_3O_3$	62.42	4.12	15.61	62.05	4.15	15.90
27	$C_{14}H_9N_3O_2$	66.93	3.61	16.73	66.88	3.81	16.48
28	$C_{14}H_{10}N_6O_2$	57.14	3.43	28.56	57.08	3.58	28.81

Scheme



stretching mode in the region 1170-1100 cm^{-1} and the typical deformation of an isolated C-H in the 890-820 cm^{-1} region, that have previously been observed for various derivatives of chromones [12,13]. For compound **27** the characteristic nitrile absorption was not observed when acquired as a potassium bromide disk, however, was observed as a weak absorption at 2230 cm^{-1} when acquired in nujol mull. This phenomenon was also observed earlier [14] and was ascribed to the absence of a contribution of the dipolar form ($-C^{+}=N^{-}$) of the cyano group when attached to an electron deficient carbon at position 6 of the molecule.

The ^{1}H-nmr spectra were consistent with the structure of these new compounds. All new compounds with the exception of **20** and **24** displayed a singlet for the proton at position-5 between δ 6.00 and 7.50 and the remaining signals correspond to the other protons contained in the various substituents. The H-5 for **20** and **24** is located within the envelop of the signals for the benzene and pyridine substituents respectively, and this shift is ascribed to the solvent effect of trifluoroacetic acid.

EXPERIMENTAL

The ^{1}H-nmr spectra were obtained on a Hitachi Perkin-Elmer model R-20B spectrometer operating at 60 MHz (tetramethylsilane as internal standard). The infrared absorption spectra were acquired on a Perkin-Elmer model 727 spectrophotometer as potassium bromide disks. Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer model 240.

4-Acetyl-5-Hydroxypyrazoles.

The following 4-acetyl-5-hydroxypyrazoles were prepared according to the method of Graham [8] from the reaction of the appropriate pyrazol-5-ones [15] with a mixture of acetic anhydride and anhydrous sodium acetate.

Method.

A mixture of 0.4 moles of the pyrazolone, 100 g of anhydrous sodium acetate and 120 ml of acetic anhydride was stirrer and heated under reflux for an hour. The cooled reaction mixture was poured onto 700 g of crushed ice and extracted with chloroform (3x200 ml). The chloroform extract was washed with cold 5% sodium hydroxite (3x500 ml). The aqeous extracts were combined and acidified with 5% hydrocloric acid, the 4-acetyl-5-hydroxypyrazole (7-10) was filtered and purified.

4-Acetyl-5-hydroxyl-3-methyl-1-phenylpyrazole (**7**).

Compound **7** had mp 60-61° (lit [8] mp 62-63°); ir (cm^{-1}): 3100 (br.OH), 1630 (C=O); ^{1}H-nmr (carbon tetrachloride): δ 2.30 (6H, s, CH_3), 7.00-7.85 (5H, m, C_6H_5), 12.85 (1H, br. OH).

4-Acetyl-5-hydroxy-l-methyl-3-phenylpyrazole (**8**).

Compound **8** has mp 89-90° recrystallized from aqueous ethanol); yield 35%, ir (cm^{-1}): 3150-3100 (br. OH), 1615 (C=O); ^{1}H-nmr (deuteriochloroform): δ 2.10 (3H, s, $COCH_3$), 3.70 (3H, s, N-CH_3), 7.35 (5H, s, C_6H_5), 10.30 (br. OH).

Anal. Calcd. For $C_{12}H_{12}N_2O_2$: C,66.65; H, 5.59; N, 12.96. Found: C, 66.95; H. 5.60: N, 12.77.

4-Acetyl-5-hydroxy-1,3-diphenylpyrazole (**9**).

Compound **9** has mp 141-142° (aqueous. ethanol); yield 23%, ir (cm^{-1}): 3100 (br.OH), 1620 (C=O); ^{1}H-nmr (carbon tetrachloride-deuteriochloroform); δ 2.15 (3H, s, $COCH_3$), 7.00-8.00 (10H, m, C_6H_5), 11.95 (br.OH).

Anal. Calcd. For. $C_{17}H_{14}N_2O_4$: C 73.37, H, 5.07; N, 10.07. Found: C, 73.44. H, 5.21; N, 9.95.

4-Acetyl-5-hydroxy-1,3-dimethylpyrazole (**10**).

Compound **10** has mp 125-126° (Sublimation); yield 45%, ir (cm^{-1}): 3270 (br. OH), 1640 (C=O); ^{1}H-nmr (deuteriochloroform): δ 2.32 (6H,s, $COCH_3$ and pyrazole CH_3), 3.54 (3H, s, N-CH_3), 7.05 (br.OH).

Anal. Calcd. For $C_7H_{10}N_2O_2$: C, 54.53, H, 6.54; N, 18.17. Found: C, 54.82; H, 6.35; N, 18.40.

1*H*-Pyrano [2,3-*c*]pyrazol-4-ones (**11-22**).

Method A.

A mixture of 1.38 g of sodium in 40 ml of ethanol was heated under reflux untill sodium was dissolved. Then 0.03 mole of a 4-acetyl-5-hydroxypyrazole was added with stirring and heating under reflux for 0.5 hour followed by addition of 30 mmoles of diethyl oxalate. The mixture was heated under reflux for another 2 hours, cooled and 3ml of concentrated sulfuric acid was cautiously added. After heating at 60-70° on a water bath for 0.5 hour, the reaction mixture was cooled and 200g of crushed ice was added to precipitate the β-diketone intermediate, which was filtered, dried and submitted to cyclization in 50 ml of dry ethanol containing 0.5 ml of concentrated sulfuric acid. After 1 hour of heating under reflux, the reaction mixture was poured onto crushed ice, the precipitate filtered and dried to give the desired esters **11** and **12** (Table 1 and 2). In the reaction of **10**, a mixture consisting of the ester and the hydrolyzed acid (**25**) was obtained, which was further hydrolyzed to give the acid (see below).

Method B.

A mixture of 5 mmoles of of acetylhydroxypyrazole and 20 mmoles of sodium hydride in 30 ml of dioxane was heated on a water bath for 0.4 hour followed by addition of 7 mmoles of an appropriate ester (ethyl acetate, ethyl benzoate, ethyl 2-furoate or ethyl nicotinate). The resulting mixture was heated under reflux for a further 4 hour period and on cooling the sodium salt of the β-diketone was precipitated by addition of ether. After 0.4 hour the precipitate was filtered off and triturated with 5% hydrochloric acid. The free β-diketone was extracted with chloroform (3x100ml), the solvent was removed and the residue was taken up in a mixture of 20 ml of sulfuric acid-acetic acid (1:10). After heating on a water bath for 2 hour the reaction mixture was poured onto crushed ice (200 g) and the precipitated product (**13-19**) was filtered off and recrystallized from a suitable solvent (Tables 1 and 2).In the case of reactions with ethyl nicotinate, the expected products ***(*20-22*)*** (Tables 1and 2) did not immediately precipitate on addition to ice and were isolated by extraction with chloroform (3x50ml), the solvent was removed and the residues were recrystallized from aqueous ethanol.

4-Oxo-1*H*-Pyrano[2,3-*c*]pyrazole-6-carboxylic Acids (**23-25**).

General Method.

A mixture of 1 g of the ester (**11, 12** or the reaction mixture of **10** with diethyl oxalate) and a mixture 20 ml of concentrated hydrochloric acid and glacial acetic acid (1:1) was heated on a water bath for 1 hour. The resulting mixture was poured onto 100 g of crushed ice and the precipitate was filtered, dried and recrystallized to yield the acids **23-25** (Tables 1 and 2).

3-Methyl-4-oxo-1-phenyl-1*H*-pyrano[2,3,-*c*]Pyrazole-6-carboxamide (**26**).

Ammonia was bubbled for 0.5 hour through a solution of 0.7 g (2.3 mmoles) of the ester **11** in 100 ml of dry ethanol at 0-5 °C. The precipitate was filtered, dried and recrystallized from ethanol to give 0.5 g of **26** (Tables 1 and 2).

3-Methyl-4-oxo-l-phenyl-1*H*-pyrano [2,3,-*c*] pyrazole-6-carbonitrile (**27**).

A mixture of 0.5 g (2 mmole) of **26,** 0.6 g of *p*-toluenesulfonyl chloride, 1 ml of pyridine and 10 ml of *N*, *N*-dimethylformamide was heated on an oil bath at 80-90 °C for 8 hours, allowed to stand overnight and then poured onto 20 g of crushed ice. The precipitate was filtered, dried and recrystallized from aqueous ethanol to give 0.42 g of **27** (Tables 1 and 2).

3-Methyl-1-phenyl-6-(tetrazol-5-yl)-1 *H*-pyrano[2,3-*c*]pyrazol-4-one (**28**).

A mixture of 0.6 g (2 mmole) of **27**, 0.15 g of sodium azide and 0.14 g of ammonium chloride in 8 ml of *N,N*-dimethylformamide was heated at 120-130 °C (equipped with calcium chloride tube) for 10 hours and left overnight. The reaction mixture was poured onto 30 g of crushed ice, acidified with 5% hydrochloric acid and the yellowish precipitate was filtered off. The product was recrystallized from a mixture of benzene and ethyl acetate to give 0.61 g of **28** (Tables 1 and 2).

Acknowledgements.

Continuous support from Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq) is gratefully acknowledged. Mario Celso Pagotto also thanks Coordenacao de Aperfeicoamento Pessoal de Nivel Superior (CAPES) for the fellowship.

REFERENCES AND NOTES

[1] M. A. Khan and A. G. Cosenza, *J Heterocyclic Chem.,* **19,** 1077 (1982) and references therein.

[2a] G. Heinisch, C. Hollub and W. Holzer, *J. Heterocyclic. Chem.,* **28,** 1047 (1991); [b] S. Gelin, B. Chantegrel and A. I. Nadi, *J Org. Chem.,* **48,** 4078 (1983).

[3] M. A. Khan, M. C. Pagotto and G. P. Ellis, *Heterocycles***, 6,** 983 (1977).

[4] A. O. Fitton and R. K. Smalley, Practical Heterocyclic Chemistry, Academic Press, London, 1968 p 24.

[5] S. Veibel, K. Eggersen and S. C. Linholt, *Acta Chem. Scand*., **8,** 768 (1954).

[6] A. Michaelis, *Ann.,* **352,** 152 (1907).

[7] N. V. Khromov-Borisov, *Zh. Obshch. Khim.,* **25,** 136 (1955).

[8] B. Graham, US Pat. 2694703 (1954); *Chem. Abstr.,* **49,** 3706 (1955).

[9] G. P. Ellis and G. Barker, *Progr. Med. Chem.,* **9,** 65 (1972).

[10] G. P. Ellis and D. Shaw, *J. Med Chem.*, **15,** 865 (1972).

[11] W. G. Finnegan, R. A. Henry and R. Lofquist, *J. Am. Chem. Soc.*, **80,** 3908 (1958).

[12] N. B. Colthup, L. H. Daly and S. E. Wiberley, Introduction to Infrared and Raman Spectroscopy, Academic Press, New York, (1964).

[13] J. H. Looker and W. W. Hanneman, *J. Org. Chem.,* **27,** 381 (1962).

[14] G. P. Ellis and D. Shaw, *J. Chem. Soc., Perkin Trans. I*, 779 (1972).

[15] L. Knorr, Ber., **16,** 2597 (1883).