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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.

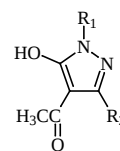
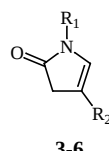
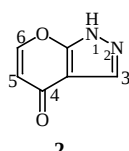
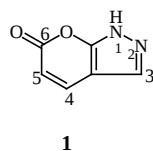
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Replacement of the benzene ring in coumarin and chromone by a pyrazole ring can lead to the heterocyclic isosteric systems 1*H*-pyrano[2,3-*c*]pyrazol-6-one (**1**) and 1*H*-pyrano[2,3-*c*]pyrazol-4-one (**2**) respectively. While **1** has been mentioned 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 Heinisch *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 ¹H-nmr spectra support the tautomeric "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 ¹H-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



3 R₁ = C₆H₅; R₂ = CH₃

4 R₁ = CH₃; R₂ = C₆H₅

5 R₁ = R₂ = C₆H₅

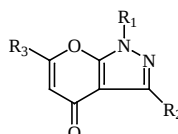
6 R₁ = R₂ = CH₃

7 R₁ = C₆H₅; R₂ = CH₃

8 R₁ = CH₃; R₂ = C₆H₅

9 R₁ = R₂ = C₆H₅

10 R₁ = R₂ = CH₃



11-28

11 R₁ = C₆H₅; R₂ = CH₃; R₃ = CO₂C₂H₅

12 R₁ = CH₃; R₂ = C₆H₅; R₃ = CO₂C₂H₅

13 R₁ = C₆H₅; R₂ = R₃ = CH₃

14 R₁ = R₃ = CH₃; R₂ = C₆H₅

15 R₁ = R₃ = C₆H₅; R₂ = CH₃

16 R₁ = CH₃; R₂ = R₃ = C₆H₅

17 R₁ = R₂ = C₆H₅; R₃ = 2-furyl

18 R₁ = C₆H₅; R₂ = CH₃; R₃ = 2-furyl

19 R₁ = CH₃; R₂ = C₆H₅; R₃ = 2-furyl

20 R₁ = R₂ = C₆H₅; R₃ = 3-pyridyl

21 R₁ = C₆H₅; R₂ = CH₃; R₃ = 3-pyridyl

22 R₁ = CH₃; R₂ = C₆H₅; R₃ = 3-pyridyl

23 R₁ = C₆H₅; R₂ = CH₃; R₃ = CO₂H

24 R₁ = CH₃; R₂ = C₆H₅; R₃ = CO₂H

25 R₁ = R₂ = CH₃; R₃ = CO₂H

26 R₁ = C₆H₅; R₂ = CH₃; R₃ = CONH₂

27 R₁ = C₆H₅; R₂ = CH₃; R₃ = CN

28 R₁ = C₆H₅; R₂ = CH₃; R₃ = 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 ₂ O 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 ₂ O 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 ₂ O 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 ₂ O 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 ₂ O 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 ₂ O 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 ₂ O 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 ₂ O 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 ₂ O 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 ₃ O 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 ₃ O 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 ₆ H ₅); 8.10-9.15(4H, m, pyridine-H) (deuteriodimethyl sulfoxide)
22	50	224-225	C ₁₈ H ₁₃ N ₃ O 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 ₆ H 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 ₂ O 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 ₆ H ₅); (deuteriochloroform-deuterio dimethyl sulfoxide)
24	69	> 300	C ₁₄ H ₁₀ N ₂ O 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 ₉ H ₈ N ₂ O 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 ₃ O 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 ₆ H ₅); 6.85 (1H, s, H-5) (deuteriodimethyl sulfoxide)
27	91	150-151	C ₁₄ H ₉ N ₃ O 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 ₆ H ₅). (deuteriochloroform)
28	87	267-268	C ₁₄ H ₁₀ N ₆ O 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 ₆ H ₅). Deutrio dimethyl sulfoxide - deuteriochloroform

[a] – in nujol

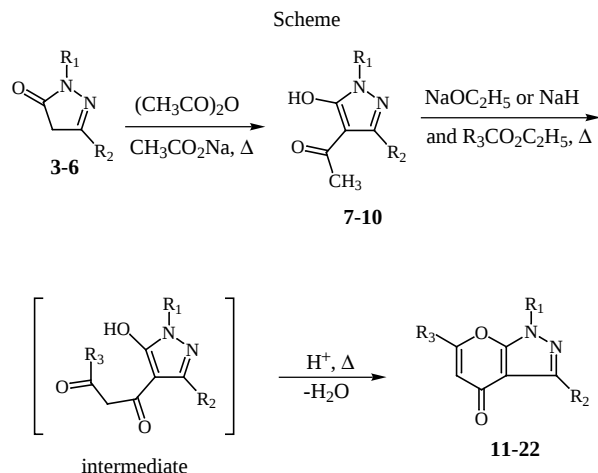
for other esters) provides an intermediate "β-diketone" which was cyclized in an acid solution to the respective 1*H*-pyrano[2,3-*c*]pyrazol-4-ones (**11-22**) [9], (Scheme). An intermediate-β-diketone from the reaction of **10** with diethyl oxalate on cyclization gave a mixture of the expected ester 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 ¹H-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 ₂ O ₄	64.42	4.73	9.39	64.31	4.80	9.45
12	C ₁₆ H ₁₄ N ₂ O ₄	64.42	4.73	9.39	64.38	4.93	9.28
13	C ₁₄ H ₁₂ N ₂ O ₂	69.99	5.03	11.66	70.08	4.94	11.66
14	C ₁₄ H ₁₂ N ₂ O ₂	69.99	5.03	11.66	70.10	5.11	11.38
15	C ₁₉ H ₁₄ N ₂ O ₂	75.48	4.67	9.27	75.13	4.77	9.33
16	C ₁₉ H ₁₄ N ₂ O ₂	75.48	4.67	9.27	75.37	4.67	9.05
17	C ₂₂ H ₁₄ N ₂ O ₃	74.57	3.98	7.91	74.31	3.86	7.64
18	C ₁₇ H ₁₄ N ₂ O ₃	69.86	4.14	9.58	69.73	4.03	9.41
19	C ₁₇ H ₁₄ N ₂ O ₃	69.86	4.14	9.58	69.95	4.01	9.35
20	C ₂₃ H ₁₅ N ₃ O ₂	75.60	4.14	11.50	75.31	4.28	11.27
21	C ₁₈ H ₁₃ N ₃ O ₂	71.26	4.32	13.85	71.02	4.30	13.68
22	C ₁₈ H ₁₃ N ₃ O ₂	71.26	4.32	13.85	70.98	4.30	13.53
23	C ₁₄ H ₁₀ N ₂ O ₄	62.22	3.73	10.37	61.92	3.74	10.27
24	C ₁₄ H ₁₀ N ₂ O ₄	62.22	3.73	10.37	61.83	3.76	10.34
25	C ₉ H ₈ N ₂ O ₄	51.93	3.87	13.47	51.71	3.65	13.37
26	C ₁₄ H ₁₁ N ₃ O ₃	62.42	4.12	15.61	62.05	4.15	15.90
27	C ₁₄ H ₉ N ₃ O ₂	66.93	3.61	16.73	66.88	3.81	16.48
28	C ₁₄ H ₁₀ N ₆ O ₂	57.14	3.43	28.56	57.08	3.58	28.81



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 ($-\text{C}^+=\text{N}^-$) of the cyano group when attached to an electron deficient carbon at position 6 of the molecule.

The ^1H -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 ^1H -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 stirred 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 hydroxide (3x500 ml). The aqueous extracts were combined and acidified with 5% hydrochloric 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); ^1H -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-1-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); ^1H -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 $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$: 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); ^1H -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 $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_4$: 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); ^1H -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 $\text{C}_7\text{H}_{10}\text{N}_2\text{O}_2$: C, 54.53, H, 6.54; N, 18.17. Found: C, 54.82; H, 6.35; N, 18.40.

1H-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 until 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 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 1 and 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-1-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).

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REFERENCES AND NOTES

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