Synthesis and Some Reactions of 3-Methyl-2-pyrazolin-4,5-dione

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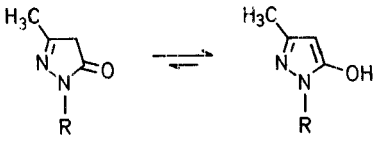
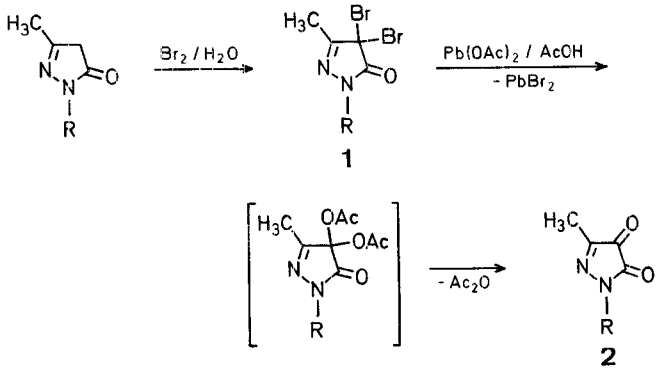
3-Methyl-2-pyrazolin-4,5-dione (**2a**) has been prepared but it was not isolated[1]. 1-Phenyl-3-methyl-2-pyrazolin-4,5-dione (**2b**) has been prepared[2] via cleavage of 1-phenyl-3-methyl-4-(4-dimethylaminophenylimino)-2-pyrazolin-5-one using sulphuric acid, water, and ether, the yield not exceeding 40%. No statement was found in the literature about the preparation of 3-methyl-2-pyrazolin-4,5-dione (**2a**) via oxidation of the corresponding pyrazolone derivative. The oxidation of 3,4-dialkyl-2-pyrazolin-5-ones with air or with *t*-butyl hydroperoxide has been found to give two different products, 3,4-dialkyl-substituted bis-pyrazolones and 3,4-dialkyl-4-hydroxy-2-pyrazolin-5-ones[3,4]. The reaction is catalyzed by copper(II) ion, catalysis being inhibited by hydrogen cations. Pyrazolones unsubstituted at N-1 consume *t*-butyl hydroperoxide; the oxidation products are oils which may result from of an oxidative or hydrolytic cleavage of the pyrazolone ring.

We have now attempted the preparation of 3-methyl-2-pyrazolin-4,5-dione derivatives by oxidation of the corresponding pyrazolone derivative using selenium dioxide but no oxidation products were obtained. This may be attributed to the strong enolisation of the pyrazolone derivative to give the 5-hydroxypyrazole analogue, a fact which supresses the reactivity of the methylene group in position 4.



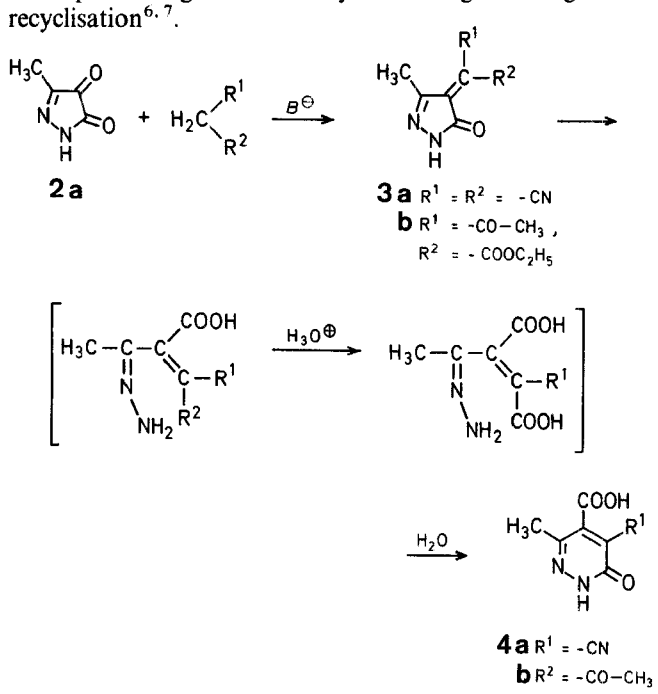
However, we succeeded in preparing 3-methyl-2-pyrazoline-4,5-dione (**2a**) and its 1-phenyl derivative (**2b**) in 71 and 68% yields, respectively, by treatment of 4,4-dibromo-3-methyl-5-oxopyrazolidine (**1a**) or its 1-phenyl derivative (**1b**) with fused lead(II) acetate in acetic acid according to the following Scheme[5]. Compound **2b** has earlier been obtained in lower yield by another method[2]. The dibromo derivatives **1a** and **1b** were obtained by bromination of the corresponding 2-pyrazolin-5-ones with bromine in water.



a R = H
b R = C_6H_5

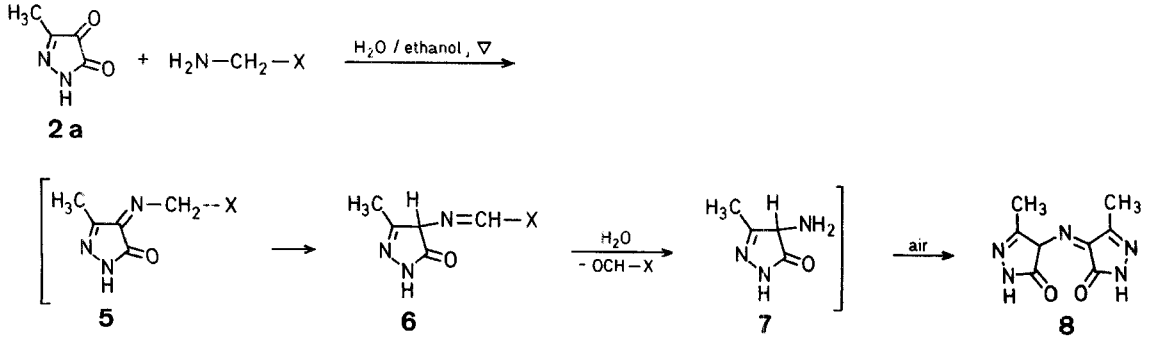
The structures of compounds **1** and **2** were proven by microanalyses and mass-, I.R.-, and ^{1}H-N.M.R.-spectral data.

The dicarbonyl compound **2a** was found to be highly reactive and can be condensed with active methylene compounds and with primary amino compounds, e.g.: amines and amino acids. The reaction with acetoacetic ester or malononitrile gives the corresponding ylidene derivative (**3**) which can be hydrolysed with mineral acids to give 5-cyano- or 5-acetyl-3-methyl-6-oxo-1,6-dihydropyridazine (**4**), the latter conversion proceeding most likely via ring cleavage and recyclisation[6,7].



The structures of compounds **3** and **4** were assigned on the basis of microanalyses and spectral data.

Compound **2a** reacts with primary aliphatic amines or with amino acids to give the same product $C_8H_9N_5O_2$ with m.p. 297 °C. The mass spectrum shows a molecular ion with m/e = 207. The ^{1}H-N.M.R.-spectrum indicates the presence of two methyl groups by a signal at δ = 2.38 ppm (s, 6H), a secondary amide proton by a signal at δ = 7.9 ppm, and an enolic proton by a signal at δ = 12.21 ppm. The I.R. spectrum shows absorption bands at 1690, 1670 and 1610 cm^{-1} which are attributable to the pyrazolone moiety[8]. The behaviour of this compound under electron impact shows the general fragmentation pathway of pyrazolones[9]. These results led us to propose the structure **8** for this product. The formation of compound **8** can be explained on the basis of a transamination reaction[10] of compound **2a** with the amino component which proceeds via the imine intermediates **5** and **6**. Air oxidation of the amino compound **7** finally affords compound **8**.



To confirm the proposed mechanism of the formation of product **8**, we prepared 4-amino-3-methyl-2-pyrazolin-5-one (**7**) by reduction of 3-methyl-4-oximino-2-pyrazolin-5-one with tin(II) chloride/hydrochloric acid. The resultant amine hydrochloride was found to be highly unstable and to be converted into compound **8** during crystallisation[11]. The identity of the two products **8** was proven by mixture m.p., microanalysis, and spectral data.

The reaction of the dicarbonyl compound **2a** with amino acids and other compounds containing the grouping CH—NH_2 was found to be general and hence may be used for both detection and quantitative estimation of such amino compounds. With amino acids, the reaction can be carried out in aqueous medium by boiling for several minutes. The precipitated product **8** shows very low solubility in lower molecular organic solvents and is insoluble in water; this enables its quantitative separation. The use of **2a** for the detection of the grouping CH—NH_2 gives more satisfactory results than the method of Ref.[12].

Melting points are uncorrected. Analytical data were obtained from Technische Hochschule Darmstadt, West Germany. Mass spectra were obtained using an AEI MS 12 mass spectrometer operating at 70 eV. The direct insertion technique was used, with a probe temperature range between 150–200 °C. The I.R. spectra were obtained on a Pye-Unicam Sp-1000 spectrometer. ^{1}H-N.M.R.-spectra were recorded on a Varian XL-100 at Technische Hochschule Darmstadt, West Germany.

3-Methyl-2-pyrazolin-5-one was prepared according to Ref.[13]; it showed analytical and spectral data in agreement with its structure.

4,4-Dibromo-3-methyl-2-pyrazolin-5-one (1a) (by a modification of the procedure of Ref.[14]):

3-Methyl-2-pyrazolin-5-one (32.6 g, 0.33 mol) is dissolved in water (600 ml) and bromine (30 ml) is added dropwise, whereupon a vigorous reaction sets in. After hydrogen bromide has ceased to evolve the solid product is isolated by suction, washed with water several times, dried. It is recrystallised from petroleum ether (60–80 °C) to give pale yellow crystals; yield: 79.9 g (94%); m.p. 132–133 °C (Ref.[14], m.p. 132 °C).

I.R. (KBr): ν = 3320 (NH); 1715 (C=O); 650 (CBr_2) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.2 (s, 3H); 3.2 ppm (s, 1H).

3-Methyl-2-pyrazoline-4,5-dione (2a):

Lead(II) acetate (30 g) is added portionwise to a stirred solution of 4,4-dibromo-3-methyl-2-pyrazolin-5-one (**1a**; 12.8 g, 0.05 mol) in glacial acetic acid (200 ml). The mixture is then heated under reflux for 10 h during which time the colour changes to deep red. The precipitated lead(II) bromide (13.9 g) is filtered off, and the clear red solution concentrated to half its volume. Product **2a** is precipitated as a red amorphous solid by the addition of ether (100 ml). It is recrystallised from ether to give red needles; yield: 3.9 g (71%); m.p. 210–212 °C.

$C_4H_4N_2O_2$	calc.	C 42.85	H 3.57	N 25.00
(112.1)	found	42.42	3.91	24.98

I.R. (KBr): ν = 3310–3300 (NH); 1700 (C=O) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.6 (s, 3H); 3.0 (s, 1H); 3.7 ppm (s, 1H).

3-Methyl-1-phenyl-2-pyrazoline-4,5-dione (2b):
This compound is prepared in an analogous manner from **1b**; yield: 68%; deep red crystals, m.p. 120–121 °C (Ref.[2], m.p. 119–121 °C).

$C_{10}H_8N_2O_2$ (188.2) calc. C 63.83 H 4.26 N 14.89
found 64.26 4.62 14.72

I.R. (KBr): ν = 1715 (C=O); 1590, 1470, 1380 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 2.2 (s, 3H); 7.5 ppm (s, $5H_{arom}$).

4-Dicyanomethylene-3-methyl-2-pyrazolin-5-one (3a):
A solution of 3-methyl-2-pyrazoline-4,5-dione (**2a**; 1.12 g, 0.01 mol), malononitrile (0.7 g, > 0.01 mol), and triethylamine (0.1 g) in absolute ethanol (25 ml) is heated under reflux for 3 h. The precipitated product is isolated by suction and recrystallised from ethanol; yield: 1.39 g (87%); deep red crystals, m.p. 263–264 °C.

$C_7H_4N_4O$ (160.1) calc. C 52.5 H 2.5
found 52.0 2.5

I.R. (KBr): ν = 3310–3350 (NH); 2200 (CN); 1690 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 1.6 (s, 3H); 3.8 ppm (s, 1H).

4-(1-Ethoxycarbonyl-2-oxopropylidene)-3-methyl-2-pyrazolin-5-one (3b):
This compound is prepared in an analogous manner using ethyl acetoacetate in place of malononitrile; yield: 85%; m.p. 187 °C.

$C_{10}H_{12}N_2O_4$ (224.2) calc. C 53.52 H 5.35 N 12.48
found 53.32 5.25 12.70

I.R. (KBr): ν = 3350–3310 (NH); 1715, 1690 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 1.6 (s, 3H); 3.8 (s, 1H); 3.0 (q, 2H); 1.29 (t, 3H); 2.03 ppm (s, 3H).

4-Carboxy-5-cyano-3-methyl-6-oxo-1,6-dihydropyridazine (4a):
A mixture of 4-dicyanomethylene-3-methyl-2-pyrazolin-5-one (**3a**; 0.8 g, 0.005 mol) and 20% sulphuric acid (20 ml) is heated under reflux for 10 h. The precipitated product is isolated by suction, washed with water, and recrystallised from acetic acid; yield: 0.62 g (69%); pale yellow crystals, m.p. 230–231 °C.

$C_7H_5N_3O_3$ (179.1) calc. C 46.90 H 2.79 N 23.46
found 46.72 2.80 23.22

I.R. (KBr): ν = 3310–3300 (NH); 2200 (CN); 1700 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 1.5 (s, 3H); 3.8 (s, 1H); 4.0 ppm (s, 1H).

5-Acetyl-4-carboxy-3-methyl-6-oxo-1,6-dihydropyridazine (4b):
This compound is prepared in an analogous manner from **3b**; yield: 62%; m.p. 285 °C.

$C_8H_8N_2O_4$ (196.2) calc. C 48.92 H 4.07 N 14.27
found 48.70 4.00 15.15

I.R. (KBr): ν = 3350–3310 (NH); 1715, 1690 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 1.6 (s, 3H); 2.03 (s, 3H); 3.8 (s, 1H); 4.0 ppm (s, 1H).

3-Methyl-4-(3-methyl-5-oxo-2-pyrazolin-4-ylidenamino)-2-pyrazolin-5-one (8):

Method A: A mixture of 3-methyl-2-pyrazolin-5-one (**2a**; 1.12 g, 0.01 mol) and benzylamine (1.072 g, 0.01 mol) in water (20 ml) + ethanol (10 ml) is heated under reflux for 20 min. The mixture is then concentrated and the precipitate obtained on cooling is isolated by suction and recrystallised from ethanol; yield: 2.02 g (98%); red needles, m.p. 295–297 °C.

$C_8H_9N_5O_2$ (207.2) calc. C 46.11 H 4.35 N 32.84
found 45.76 4.42 32.53

M.S.: m/e = 207 (M^+).

I.R. (KBr): ν = 1690, 1670, 1610 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 2.38 (s, 6H, $2CH_3$); 7.9 (s, 1H, NH); 12.21 ppm (s, 1H, enolic OH).

Similar results in the synthesis of compound **8** are obtained when benzylamine is replaced by methylamine, ethylamine, propylamine, isopropylamine, butylamine, isobutylamine, cyclohexylamine, glycine, alanine, valine, leucine, phenylalanine, or tyrosine.

Method B: A mixture of 3-methyl-4-oximino-2-pyrazolin-5-one (6.35 g, 0.05 mol) and tin(II) chloride (18.9 g, 0.1 mol) in hydrochloric acid (100 ml) is heated under reflux until colourless. The mixture is then filtered and air is bubbled through it for 30 min. The precipitated compound **8** is isolated by suction and recrystallised from ethanol to give pure **8** which is identical in all respects with compound **8** prepared by Method A; yield: 7.25 g (70%).

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