Preparation and Oxidation of 1-Hydroxypyrazoles and 1-Hydroxypyrazole 2-Oxides

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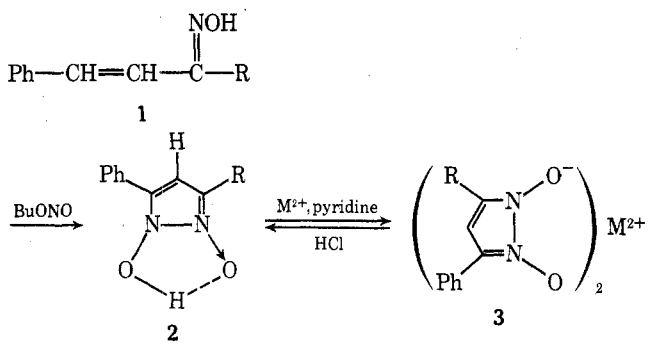
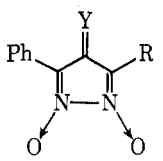
Nitrosation of α,β-unsaturated oximes in the presence of appropriate metal ions permits the isolation as their metal complexes of two new 1-hydroxypyrazole 2-oxides **2** which are unsubstituted at C-4. Reduction of **2** gives the corresponding 1-hydroxypyrazoles **7**. Both **2** and **7** may be oxidized with Fremy's salt to give 3,4-diazacyclopentadienone derivatives.

The nitrosation of benzalacetone oxime (**1a**) using butyl nitrite gives the 1-hydroxypyrazole 2-oxide **2a** which may be isolated as the insoluble metal complex **3a** when the reaction is carried out under mildly basic conditions in the presence of an appropriate metal ion.[1] We wish to report the further investigation of this reaction, its extension to the preparation of **2b** from chalcone oxime (**1b**), the reduction of **2** to 1-hydroxypyrazoles, and the behavior of 1-hydroxypyrazoles and 1-hydroxypyrazole 2-oxides under oxidizing conditions.



a, R = Me
b, R = Ph

Treatment of **1a** in aqueous ethanol containing 1 equiv of pyridine and an excess of an appropriate metal ion with butyl nitrite leads to the formation of **2a.** Consistent with the behavior of the known 1-hydroxypyrazole 2-oxides,[2,3] pyridine converts **2a** into its conjugate base which precipitates as an insoluble complex with the metal ion. By removing **2a** as its complex it is possible to avoid the facile reactions of **2a** under nitrosation conditions which preclude its isolation in the absence of the metal.[1,4-6] Initial studies of this novel complexation method involved the use of cobaltous chloride, but subsequent investigation shows that the divalent ions of zinc, nickel, and manganese behave in a manner similar to cobalt, giving the corresponding complexes **3a,** which can be converted to **2a** by treatment with hydrochloric acid. In each case, however, some quantities of by-products identified as the known 3,4-diazacyclopentadienone 3,4-dioxide derivatives **4** and **5** were obtained. Since **4** and **5** are the usual products



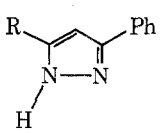
4, Y = O
5, Y = NOH

obtained when the nitrosation is carried out in the absence of the metal ion, it would appear that with these ions, the formation of the complex is not rapid enough to remove **2a** completely before further reaction occurs or else complexation is sufficiently reversible to provide some concentration of **2a** in equilibrium. Our experience suggests that both of these factors may be involved.

Copper(II) was found to be superior in effecting the isolation of **2a.** While the reactions run with the other metals typically gave yields of 25–40%, a yield of about 70% of **2a** was realized when copper sulfate was used. In addition to the higher yield obtained in this instance, the crude product was essentially free of the by-products observed in the other reactions. The advantage of copper over the other metals in this case would appear to be due to its superior ability to complex with the conjugate base of **2a.**

The synthetic procedure was extended to the nitrosation of chalcone oxime (**1b**), once again using a variety of metal ions. In this instance the most satisfactory results were obtained using cobalt(II), with which yields of about 40% of **2b** could be isolated. When copper(II) was used in this case, nitrosation was very sluggish, and low yields of the metal complex were observed. Since a marked color change from blue to dark green occurs when solutions of the unsaturated oximes are mixed with aqueous solutions of copper sulfate and pyridine, it seems likely that a copper complex with **1b** is formed which may explain the decreased reactivity. There is a considerable body of chemical literature describing the formation of complexes between oximes and metals, and it is certainly not surprising to observe such behavior in this instance. The choice of the best metal ion for the isolation of **2** would seem to be dictated by several factors, only one of which is the ability of the metal to complex with the pyrazole. Thus far attempts to extend this method to the isolation of the 3,5-dimethyl analogue of **2** have been unsuccessful. Studies of the complexation of **1** and **2** with metal ions are in progress which may help to elucidate the exact role of the metal in the reaction and to reveal the factors which determine the best choice of metal for a given case.

The identification of **2a** has been discussed in an earlier communication, and similar evidence is invoked in the assignment of the structure of **2b.** In addition to its chemical behavior (acidity, formation of metal complexes), **2b** gave a satisfactory elemental analysis. The infrared spectrum of **2b** closely resembled those of known 1-hydroxypyrazole 2-oxides,[2] and the NMR spectrum was completely consistent with the assigned structure. Finally, the parent 3,5-diphenylpyrazole **6b** could be obtained by reduction of **2b** with zinc in acetic acid.



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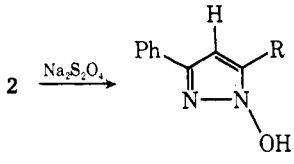
The reduction of 1-hydroxypyrazole 2-oxides with sodium dithionite is reported to yield 1-hydroxypyrazoles,[2] and the compounds **2a** and **2b** were reduced in this way to **7a** and **7b.** It is of interest that only one of the two possible isomeric 1-

hydroxypyrazoles, **7a**, is obtained when **2a** is reduced. Even though the yield of **7a** is rather low, careful investigation of



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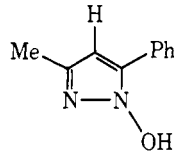
the crude product reveals none of the isomeric **8**, at least within the limits of detection by NMR analysis. The identification of **7a** and **7b** followed from their elemental analyses, spectra, and reduction with zinc in acetic acid to the parent pyrazoles, **6**. The oxidation of **7** to known compounds which will be discussed below not only provides further evidence for the assigned structures, but also allows the unambiguous assignment of **7a** rather than **8**. The regiospecificity of the di-



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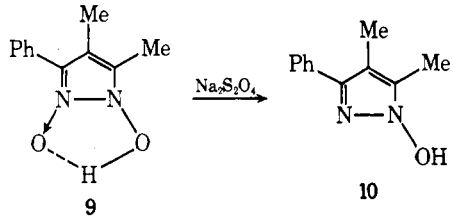
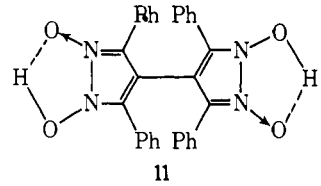
thionite reduction of 1-hydroxypyrazole 2-oxides is not without precedent, since Freeman and Gannon have reported that the reduction of **9** yields only a single product assigned as **10**.[2]



9 **10**

A principal consideration in undertaking the synthesis of **2a** and **2b** was an interest in the effect of the oxygen functions on the reactivity of the pyrazole ring. This effect includes an apparently enhanced susceptibility of the ring to electrophilic substitution and also toward free-radical oxidation as suggested by the interesting products, **4** and **5**, formed when **1** is nitrosated in aqueous acetic acid, and also by the novel dimer, **11**, which is formed when **1b** is treated with amyl nitrite in



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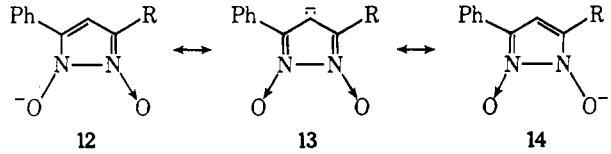
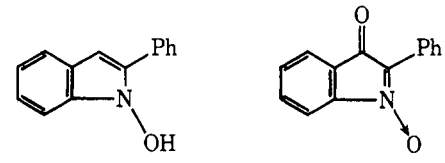
methanol.[6] All of these reactions suggest that the 1-hydroxyl group exerts an activating effect on the pyrazole ring which is analogous to the effect of the hydroxyl group on the reactivity of aromatic rings in phenols. This effect might be expected to be even more important for the conjugate base of **2**, for which contributing structures **12**, **13**, and **14** are possible.



12 **13** **14**

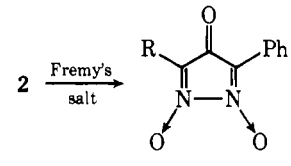
These structures suggest a particularly high electron density and potential reactivity at C-4, which is precisely the site available for study in **2**.

Precedent for the activating effect of an *N*-hydroxyl group in azole oxidation may be seen in the conversion of the 1-hydroxyindole **15** to phenylisatogen (**16**) in low yield by amyl



15 **16**

nitrite,[7] lead(IV) acetate,[8] and air,[9] and in nearly quantitative yield by *p*-nitroperbenzoic acid.[10] A similar oxidation has been proposed as the origin of the ketone **4** when the nitrosation of **1** is carried out in aqueous acid. In order to investigate the ease of oxidation of **2**, Fremy's salt (potassium nitrosodisulfonate) was chosen as a very mild free-radical oxidizing agent which has been widely applied for the selective oxidation of phenols to quinones.[11,12] It was observed that treatment of buffered aqueous solutions of **2a** and **2b** with Fremy's salt did, indeed, give the corresponding 3,4-diazacyclopentadienone 3,4-dioxides, **4**.



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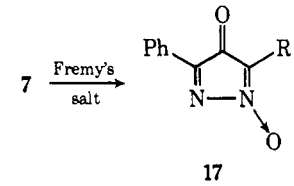
The 1-hydroxypyrazoles, **7**, also react readily with Fremy's salt, giving the respective 3,4-diazacyclopentadienone 3-oxides, **17**. Both **17a** and **17b** are known compounds which were



17

identified by independent synthesis. The structure of **17a** is of particular interest, since it has been demonstrated unequivocally that the methyl group is located on the carbon atom of the nitrone function as shown.[13] This serves to establish the location of the methyl group at C-5 in the 1-hydroxypyrazole **7a**.

The above results establish that the 1-hydroxypyrazoles are appreciably activated toward oxidation under free-radical conditions as has been predicted. With the ready availability of substantial quantities of **2a** and **2b** and also of **7a** and **7b**, we are pursuing further investigations into the effect of N-oxygenation on the reactivity of the pyrazole ring.

Experimental Section

The NMR spectra were obtained using a Hitachi Perkin-Elmer R20 60-MHz spectrometer, and chemical shifts are reported as δ in parts per million relative to tetramethylsilane as an internal standard. Melting points were taken in open capillaries using the Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Clark, Means, and Perkins Microanalytical Laboratory, Urbana, Ill.

5-Methyl-3-phenyl-1-hydroxypyrazole 2-Oxide (2a). A solution of 125 g (0.5 mol) of $CuSO_4 \cdot 5H_2O$ in 500 ml of water and 40 g (0.5 mol) of pyridine was added to a solution of 80.5 g (0.5 mol) of 4-phenyl-3-buten-2-one oxime (**1a**) in 1000 ml of 95% ethanol. The temperature was adjusted to about 35 °C and 56.7 g (0.55 mol) of butyl nitrite was added in one portion. The resulting solution was stirred at 35–40 °C for 2 h, cooled in ice, and the brown copper complex was filtered off and washed with 150 ml of cold ethanol–water (2:1) and then with water until the wash was colorless. The solid was added in portions to a stirred beaker of 1000 ml of warm HCl (concentrated), and when nearly all of the solid had dissolved the solution was filtered and the

filtrate was diluted with 2000 ml of water and cooled. The precipitate was collected, pressed dry, and washed under suction with water until the wash was colorless. The moist solid was dissolved with warming in a solution of 20 g of NaOH in 500 ml of 80% ethanol. The solution was treated with 5 g of activated charcoal, heated for 10 min, and filtered through Celite. The filtrate was acidified with 35 ml of acetic acid, cooled overnight, and the product was collected and washed with ethanol, then repeatedly with water, and again with ethanol. Concentration of the filtrate and dilution with water gave a small second crop. After drying in vacuo over P_2O_5, the yield was 69.7 g (73%) of white solid: mp 181–182 °C dec; NMR (CF_3CO_2H) δ 7.80–8.90 (m, 5 H, C_6H_5), 6.47 (s, 1 H, pyrazole C-4 proton), 2.52 (s, 3 H, CH_3).

An analytical sample was prepared by careful precipitation from the potassium salt in ethanol solution upon acidification with acetic acid.

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.88; H, 5.35; N, 14.54.

The potassium salt of **2a** was generated with an ethanolic solution of KOH and was recrystallized from tetrahydrofuran–ether as white needles, mp 182–186 °C. This material picked up water of hydration on standing and was dried just prior to analysis at 80 °C under vacuum.

Anal. Calcd for $C_{10}H_9N_2O_2K$: C, 52.61; H, 3.98; N, 12.26. Found: C, 52.80; H, 4.16; N, 12.08.

The cobalt complex of **2a** was prepared by treating an aqueous solution of the potassium salt with a slight excess of an aqueous solution of cobaltous chloride. The violet solid was collected by filtration and washed with water, methanol, and acetone to give **3a** (M = Co), mp 228 °C dec.

Anal. Calcd for $C_{20}H_{18}N_4O_4Co$: C, 54.92; H, 4.16; N, 12.81. Found: C, 54.56; H, 4.14; N, 13.06.

3,5-Diphenyl-1-hydroxypyrazole 2-Oxide (2b). A solution of 11.15 g (0.05 mol) of chalcone oxime in 100 ml of 95% ethanol was treated with a solution of 12 g (0.05 mol) of $CoCl_2 \cdot 6H_2O$ in 20 ml of water and 4.0 g (0.05 mol) of pyridine. The temperature was adjusted between 35 and 40 °C and 5.5 g (0.055 mol) of butyl nitrite was added over 30 min to the stirred solution. After stirring for 5 h at 35–40 °C an additional 2 g of butyl nitrite was added, and stirring was continued for 2 h. The solid was filtered off and the filtrate was diluted to 400 ml with water and treated with 200 ml of ether. The insoluble material was filtered off and added to the original solid, and the combined solids were stirred for 3 h with 150 ml of 4 N HCl. The product was filtered off and washed with water and with ethanol and dried to yield 4.88 g (39%) of tan solid. The material could be purified by reprecipitation from aqueous base. An analytical sample was prepared by careful precipitation from the recrystallized potassium salt (mp 280–282 °C) and had mp 199–200 °C dec; NMR (CF_3CO_2H) δ 7.20–8.20 (m, 10 H, C_6H_5), 6.85 (s, 1 H, pyrazole C-4 proton).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.59; H, 4.94; N, 11.01.

5-Methyl-3-phenyl-1-hydroxypyrazole (7a). To a solution of 9 g of sodium dithionite in 150 ml of water was added 2.2 g (10 mmol) of the potassium salt of **2a.** The mixture was warmed on a steam bath overnight, cooled in ice, and filtered. The white solid was recrystallized to yield 0.3 g (17.4%) of **7a:** mp 198–199 °C dec; NMR (CF_3CO_2H) δ 7.40–7.70 (m, 5 H, C_6H_5), 6.62 (s, 1 H, pyrazole C-4 proton), 2.51 (s, 3 H, CH_3).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.07. Found: C, 69.38; H, 6.08; N, 15.73.

3,5-Diphenyl-1-hydroxypyrazole (7b). A solution of 0.90 g (3 mmol) of the potassium salt of **2b** in 25 ml of water was added to a solution of 6.0 g of sodium dithionite in 100 ml of water and the mixture was warmed on a steam bath for 18 h. After cooling, the solid was filtered off and recrystallized from 2-propanol–water to give white crystals: mp 170–171 °C; NMR ($CDCl_3$) δ 11.35 (s, 1 H, OH), 7.0–8.0 (m, 10 H C_6H_5), 6.50 (s, 1 H, pyrazole C-4 proton).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.27; H, 5.13; N, 11.85. Found: C, 76.27; H, 5.10; N, 11.78.

Reduction of 2 and 7 with Zinc. In a typical reaction, 1.0 g of the oxygenated pyrazole and 5 g of zinc powder were stirred under reflux in acetic acid for 30 min. The mixture was filtered, and the filter cake was washed with methanol. The filtrate was evaporated under reduced pressure, and the residue was washed with water, recrystallized from ethanol, and sublimed. Reduction of **2a** and **7a** gave 3(5)-methyl-5(3)-phenylpyrazole (**6a**), identical with an authentic sample,[14] while **2b** and **7b** yielded 3,5-diphenylpyrazole (**6b**), which was also compared with an authentic sample.[15]

Oxidation of 2a and 2b with Fremy's Salt. A solution of 1.0 mmol of the potassium salt of the 1-hydroxypyrazole 2-oxide in 25 ml of water was added at room temperature to a stirred solution of 0.8 g of Fremy's salt[12] in 50 ml of water buffered with 1.14 g of $K_2HPO_4 \cdot 3H_2O$ and stirred. When the purple color was discharged, additional portions of Fremy's salt were added until the color persisted. The mixtures were cooled, and the products recovered by filtration. The yield of **4a,** mp 164–165 °C, was 60%, while that of **4b,** mp 192–194 °C, was 64%. The products were identified by comparison with authentic samples.[5]

Oxidation of 7a and 7b with Fremy's Salt. A solution of 0.5 g of the 1-hydroxypyrazole in 50 ml of CH_2Cl_2 was treated with 50 ml of a 5% solution of $K_2HPO_4 \cdot 3H_2O$ and stirred at room temperature while 2.5 g of Fremy's salt was added. Stirring was continued until reaction was complete (TLC), and then the organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated. The residual solid was washed with petroleum ether and recrystallized. The yield of **17a** was 41%, while that of **17b** was 90%. The products were identified by comparison with authentic samples.[5]

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Registry No.—**1a,** 2887-98-1; **1b,** 6502-38-1; **2a,** 55026-66-9; **2a** K salt, 59434-81-0; **2b,** 59434-82-1; **2b** K salt, 59434-83-2; **3a,** 59448-48-5; **4a,** 16901-38-5; **4b,** 17952-96-4; **7a,** 59434-84-3; **7b,** 59434-85-4; cobaltous chloride, 7646-79-9.

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