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Nitrosation of acrylophenone oxime or of methacrylophenone oxime with *n*-butyl nitrite in the presence of pyridine and copper(II) sulfate gives the copper complexes of the title compounds. The free 1-hydroxypyrazole 2-oxides are isolated by treating the copper complexes with dilute sodium hydroxide, filtration, and acidification of the basic filtrates. The title compounds are the first examples of 1-hydroxypyrazole 2-oxides in which the C3(5) ring position is unsubstituted.

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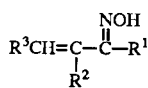
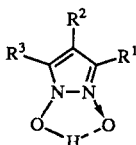
The nitrosation α,β -disubstituted vinyl ketoximes such as **1a** using sodium nitrite and acetic acid has been reported by Freeman [1] to provide a convenient route to 3,4,5-trisubstituted-1-hydroxypyrazole 2-oxides, *e.g.* **2a**. Applying similar nitrosation conditions to β -monosubstituted vinyl ketoximes of type **1b** gave 4-pyrazolone 1,2-dioxides, which were believed to be formed through the intermediacy of 3,5-disubstituted-1-hydroxypyrazole 2-oxides, in this case **2b** [2]. Subsequently we were able to isolate **2b** as its copper complex by nitrosation of **1b** with *n*-butyl nitrite in aqueous ethanol in the presence of pyridine and copper(II) sulfate. The free pyrazole could be liberated from the copper complex by treatment with hydrochloric acid [3,4]. We now wish to report the extension of this methodology to the nitrosation of methacrylophenone oxime **1c** and acrylophenone oxime **1d**, to produce new 1-hydroxypyrazole 2-oxides **2c** and **2d**, the first examples of

this system in which the one of the positions adjacent to nitrogen in the pyrazole ring, C3 or C5, is unsubstituted [5].

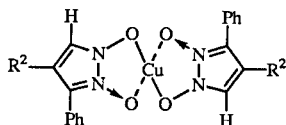
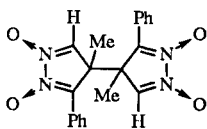
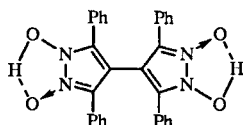
The nitrosation reactions of **1c** and **1d** were carried out by treating the oximes in ethanolic solution with aqueous copper(II) sulfate, followed immediately by addition of pyridine and *n*-butyl nitrite. Upon standing for several hours at room temperature the crystalline, olive-green copper complexes separated and were isolated by suction filtration. Treatment of the filtrate with water and ether followed by stirring for several minutes caused separation of small second crops of the copper complexes. The copper complexes were assigned as **3c** and **3d**, respectively, on the basis of satisfactory elemental analyses and by analogy with the complexes of other 1-hydroxypyrazole 2-oxides.

Attempts to liberate the free 1-hydroxypyrazole 2-oxides from the copper complexes by treatment with hydrochloric acid as had been done in the preparation of **2b** [4] were unsuccessful. Under mild conditions the complexes were recovered unchanged, and under more vigorous conditions the pyrazoles decomposed. It was found, however, that the copper complexes were cleanly and rapidly dissociated by stirring for a few minutes in aqueous ethanol with an excess of dilute sodium hydroxide. After filtration to remove inorganic material, the basic solutions were cooled in ice and acidified, whereupon **2c** or **2d** precipitated, to be recovered by suction filtration.

The identification of **2c** and **2d** as the desired 1-hydroxypyrazole 2-oxides followed from satisfactory elemental analyses for the free heterocycles and for the copper complexes, and from infrared and nuclear magnetic spectral properties which were consistent with the assigned structures. The infrared spectra of the new compounds resembled those of other previously reported 1-hydroxypyrazole 2-oxides. The ir spectra of these compounds are very distinctive, being characterized by an envelop of broad bands in the region of 1000 to 2000 cm^{-1} , with a few sharper bands at higher and lower frequency. The pmr spectra of **2c** and **2d** in deuteriochloroform included signals for the OH protons in the region of δ 13-14 ppm, consistent

**1****2**

- a** ($\text{R}^1 = \text{R}^3 = \text{Ph}$, $\text{R}^2 = \text{Me}$)
- b** ($\text{R}^1 = \text{R}^3 = \text{Ph}$, $\text{R}^2 = \text{H}$)
- c** ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$)
- d** ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{R}^3 = \text{H}$)

**3e** ($\text{R}^2 = \text{Me}$)**3d** ($\text{R}^2 = \text{H}$)**4****5**

with very strong deshielding for the chelated protons. The signals for the protons at the C3(5) position appeared at δ 7.15 and 7.35 for **2c** and **2d**, respectively. The spectrum of **2c** included a three-proton singlet at 2.15 ppm for the methyl group, while the signal for the proton at C4 in **2d** appeared at δ 6.35, which compared well with a value of 6.17 for the proton at C4 in a sample of **2b** [6] which was run for comparison. In the cmr spectra the signal for C4 of the pyrazole ring appears at 106.54 for **2c** and at 95.82 for **2c**. The carbon atoms at C3 and C5 in **2c** and **2d** give signals which are broadened by coupling with the nitrogen atoms; of these, the signals for the carbon atoms bearing the phenyl substituents appear at δ 129.5 and 131.1 for **2c** and **2d**, while the signals for the unsubstituted pyrazole carbons appear at δ 118.05 and 118.7 ppm.

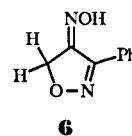
Like other 1-hydroxypyrazole 2-oxides, **2c** and **2d** were relatively acidic and formed stable, crystalline salts upon treatment with ethanolic sodium hydroxide. Of particular note in the pmr spectra of the salts (run in deuterium oxide) was the appearance of the signals for the protons located at C4 and C5 for the sodium salt of **2d**. In the free pyrazole, the signals for those two protons appeared as singlets, while in the spectrum of the sodium salt coupling could be observed, and the signals appeared as doublets, $J = 2.9$ Hz, at 6.36 (C4 proton) and 6.97 ppm (C5 proton). Also, in the cmr spectra of the salts the signals for C3 and C5 did not exhibit the broadening ascribed to coupling with nitrogen which was seen for the free pyrazoles.

The ether-soluble material obtained from the nitrosation of **1c** contained one principal byproduct, formed in about 6% yield. Although elemental analysis results were consistent with an empirical formula of $C_{10}H_9N_2O_2$, there is no reasonable structure which would fit that formula. Rather, the most likely structure for this compound is the 4,4'-bipyrazole 1,1',2,2'-tetraoxide **4**. The symmetrical structure of **4** is consistent with the cmr spectrum, which contained eight signals. The pmr spectrum contains a single signal for the equivalent methyl groups at δ 1.82, a signal at 5.19 for both protons at C5 and C5', and signals for two equivalent phenyl groups. Further, it was found that **4** could be obtained as the principal product when a sample of **2c** was treated with *n*-butyl nitrite in ethanol. The formation of **4** in this reaction has an analogy in the formation of the 1,1'-dihydroxy-4,4'-bipyrazole 2,2'-dioxide derivative **5** upon nitrosation of chalcone oxime [7,8]. Compound **4**, like **5**, can be accounted for by oxidative coupling of 1-hydroxypyrazole 2-oxides at C4. Although **4** could exist in two diastereomeric modifications, we have isolated only one form from this reaction, and there is no indication that any significant amount of a second form is present, at least within the limits of detection by nmr analysis.

In the case of the nitrosation of **1d**, the ether-soluble

fraction contained a byproduct isolated as a colorless solid in 3% yield. This was assigned as the 4-isoxazolone oxime **6**. We have observed 4-isoxazolone oximes as byproducts in the nitrosation of other unsaturated ketoximes [9], and such compounds have also been reported by another investigator [10]. The identification of **6** is based upon its elemental analysis, an infrared spectrum which includes an OH stretching absorption at 3182 cm^{-1} , and its pmr spectrum, which consists of a broad singlet at δ 8.18 (1H, exchangeable by deuterium oxide, OH), signals for the five protons of the phenyl group, and a two-proton singlet at 5.20 for the protons located at C5. Although geometric isomerism about the oxime double bond is possible, only one form of **6** is observed.

The results described above indicate that nitrosation of α,β -unsaturated ketoximes may be extended to the preparation of 3(5),4-disubstituted-1-hydroxypyrazole 2-oxides and 3(5)-substituted-1-hydroxypyrazole 2-oxides. These compounds are of interest to us, because their availability makes it possible for the first time to investigate the influence of the vacant C5 position on the reactivity of 1-hydroxypyrazole 2-oxides. We are preparing further examples of 1-hydroxypyrazole 2-oxides which lack substituents at C5 and are studying their reactivity.



EXPERIMENTAL

The ir spectra were run as nujol mulls using a Nicolet 5SXC FT-IR Spectrometer; nmr spectra were run on a Varian Gemini-300 Spectrometer in deuteriochloroform with tetramethylsilane as an internal standard, except for the sodium salts, which were run in deuterium oxide with sodium 3-trimethylsilylpropanesulfonate as the standard. Elemental analyses were done by Micro-Analysis, Inc., Wilmington, DE; mp values were obtained with a Thomas Hoover Uni-melt apparatus and are uncorrected.

Copper(II) Complex **3c** of 4-Methyl-3(5)-phenyl-1-hydroxypyrazole 2-Oxide.

A solution of methacrylophenone oxime [11], 3.22 g (20 mmoles), in 40 ml of ethanol (95%) was treated in a single portion with a solution of 5.0 g (20 mmoles) of copper(II) sulfate pentahydrate in 20 ml of water, followed in rapid succession by 3.2 g (40 mmoles) of pyridine and 3.1 g (30 mmoles) of *n*-butyl nitrite. After standing overnight at room temperature the mixture was cooled in ice, and a crystalline, olive-green solid, **3c**, was collected and washed with 100 ml of water, 50 ml of ethanol, and 100 ml of ether. The filtrate and wash solutions were combined, treated with an additional 100 ml of water and 100 ml of ether, stirred for 20 minutes at room temperature, and an additional small portion of **3c** was collected. The yield of **3c**, mp 209° dec was 3.95 g (89%); ir: 3144 cm^{-1} (ν C-H for H attached to C3(5)), 1334, 901,

767, 755, 695, 603 cm^{-1} .

Anal. Calcd. for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_4\text{Cu}$: C, 54.36; H, 4.10; N, 12.68. Found: C, 54.51; H, 4.06; N, 12.56.

The filtrate was treated with 25 ml of 1.5 *M* hydrochloric acid, and the ether layer was separated, washed with 25 ml of 1.5 *M* hydrochloric acid, two 25 ml portions of 5% sodium carbonate, and 50 ml of saturated sodium chloride, dried (sodium sulfate), and evaporated. The residual tan solid was recrystallized from ethanol (95%) to give 0.23 g (6%) of **4** as colorless needles, mp 208-209° dec; ir: 1579, 1570, 1369, 1145, 750, 694, 613 cm^{-1} ; pmr: δ 8.10 (d, *J* = 7.3 Hz, 4H) and 7.3-7.4 (m, 6H) (Ph), 5.19 (s, 2H, C5 and C5' protons), 1.82 (s, 6H, Me groups); cmr: δ 130.36, 128.47, 127.59, 125.29, 123.25, 93.24, 79.65, 21.80.

Anal. Calcd. for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_4$: C, 63.48; H, 4.79; N, 14.81. Found: C, 63.26; H, 4.87; N, 14.68.

4-Methyl-3(5)-phenyl-1-hydroxypyrazole 2-Oxide (**2c**).

The copper complex **3c**, 3.95 g (8.9 mmoles), from above was suspended in 50 ml of ethanol-water (1:4), treated with 25 ml of 5% sodium hydroxide solution, and stirred at room temperature. After 20 minutes the mixture was filtered, and the inorganic residue washed with water. The filtrate and wash were combined, cooled in ice, and acidified to Congo red with concentrated hydrochloric acid. After standing in ice for several minutes, the finely divided, colorless precipitate was collected, washed several times with portions of cold water, pressed dry under suction, and dried to constant weight under vacuum. The yield of **2c**, a colorless solid, mp 134-136° dec was 3.02 g (89%); ir: 3195 cm^{-1} (strong, sharp), 1515, 1416, 1363, 1239, and 1182 (strong, broad), 941, 781, 751, and 689 (strong, sharp); pmr: δ 14.12 (br s, 1H, OH), 7.4-7.6 (m, 5H, Ph), 7.15 (s, 1H, C3(5) proton), 2.15 (s, 3H, Me); cmr: δ 129.53 (broad), 129.27, 128.99, 128.55, 126.71, 118.05 (broad) (unsubstituted C3(5)), 106.54 (C4), 9.86 (Me). An analytical sample was prepared by reprecipitation from the sodium salt, washed with cold water, and dried under vacuum.

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.29; H, 5.36; N, 14.65.

The sodium salt of **2c** was produced by suspending a sample in ethanol (absolute) about 5 ml per g of solid, treating the mixture with a slight excess of 50% aqueous sodium hydroxide and warming to obtain a homogeneous solution. Dilution with ether and cooling gave the sodium salt as cream-colored crystals, which were recrystallized from ethanol-water. Water of hydration was retained even after drying at 80° under 0.2 torr overnight; the salt had mp 226-228° dec; ir: 3229 cm^{-1} (broad, H_2O), 3142, 1689 (weak), 1371, 1304, 1110, 897, 755, 695, 664; pmr: δ 7.4-7.6 (m, 5H, Ph), 6.97 (s, 1H, C3(5) proton), 1.99 (s, 3H, Me); cmr: δ 131.81, 131.22 (a shoulder on the downfield side of this signal may be the unresolved signal for the C not otherwise accounted for), 130.83, 126.94, 115.42 (unsubstituted C3(5)), 107.17 (C4), 11.56 (Me).

4,4'-Dimethyl-3,3'-diphenyl-4,4'-(bi-4*H*-pyrazole) 1,1',2,2'-Tetraoxide (**4**).

A suspension of **2c**, 0.38 g (2 mmoles), in 15 ml of ethanol (95%) was treated with 0.26 g (2.5 mmoles) of *n*-butyl nitrite and stirred at room temperature for 60 minutes. As **2c** dissolved, it was replaced by fine colorless needles. The reddish mixture was cooled and the colorless solid collected and washed with cold ethanol to give 0.23 g (63%) of **4**, identical with the byproduct described above.

Copper(II) Complex **3d** of 4-Methyl-3(5)-phenyl-1-hydroxypyra-

zole 2-Oxide.

The nitrosation of 2.94 g (20 mmoles) of **2d** [12] was carried out in the same way as described for **2c** above. This gave **3d**, 1.56 g (38%), as olive-green crystals, mp 208° dec; ir: 3147 cm^{-1} and 3120 (ν C-H for H atoms attached to pyrazole ring), 1493, 1389, 1282, 957, 783, 764, 735, 684.

Anal. Calcd. for $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_4\text{Cu}$: C, 52.24; H, 3.41; N, 13.54. Found: C, 51.95; H, 3.31; N, 13.34.

Treatment of the ether layer as described above gave, after evaporation, 0.23 g of a brown, oily solid. Preparative thin layer chromatography on silica gel (EM Silica Gel 60 F₂₅₄, 2 mm, 20 x 20 cm) with chloroform gave one major component which was extracted with acetone from a band at *R_f* 0.15-0.35. Recrystallization from benzene gave 0.09 g (3%) of **6** as a colorless, crystalline solid, mp 170-171°; ir: 3182 cm^{-1} (broad, ν O-H), 1655 (weak, ν C=N), 958, 895, 769; pmr: δ 8.18 (br s, 1H, OH), 8.03 (d, *J* = 7.3 Hz, 2H) and 7.4-7.5 (m, 3H) (Ph), 5.20 (s, 2H, C5 protons); cmr: δ 159.88 (C3), 152.38 (C4), 130.59, 128.60, 127.71, 126.77, 71.01 (C5). An analytical sample was sublimed at 90° and 0.2 torr, mp 170-171°.

Anal. Calcd. for $\text{C}_9\text{H}_8\text{N}_2\text{O}_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.35; H, 4.70; N, 15.66.

3(5)-Phenyl-1-hydroxypyrazole 2-Oxide (**2d**).

The copper complex **3d**, 1.56 g (3.8 mmoles), was treated with dilute sodium hydroxide in ethanol-water as described above for **3c**. The colorless, finely divided solid was collected and dried under vacuum to give 1.17 g (87%) of **2d**, mp 120-122° dec; ir: 3135 cm^{-1} (strong, sharp), 1513, 1415, 1365, 1240, and 1182 (strong, broad), 941, 761, 751, and 689 (sharp); pmr: δ 13.08 (br s, 1H, OH), 7.90 (d, *J* = 7.2 Hz, 2H) and 7.4-7.5 (m, 3H) (Ph), 7.35 (s, 1H, H at C3(5)), 6.35 (s, 1H, H at C4). An analytical sample was prepared by acidic reprecipitation from an aqueous solution of the sodium salt, washed with water and dried under vacuum.

Anal. Calcd. for $\text{C}_9\text{H}_8\text{N}_2\text{O}_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.29; H, 4.75; N, 15.97.

The sodium salt of **2d** was generated with aqueous ethanolic sodium hydroxide as described for **2c** and recrystallized from ethanol-ether as cream-colored crystals, mp 237-238° dec. It retained water of hydration even after drying overnight at 80° under 0.2 torr; ir: 3190 cm^{-1} (broad, H_2O), 3142, 1605 (moderate), 1496, 1379, 1271, 1050, 791, 760, 705 (very strong), 655; pmr: δ 7.91 (d, *J* = 7.7 Hz, 2H) and 7.35-7.55 (m, 3H) (Ph), 7.08 (d, *J* = 2.9 Hz, 1H, H at C3(5)), 6.36 (d, *J* = 2.9 Hz, 1H, H at C4); cmr: δ 131.76, 131.46, 130.71, 128.88, 127.75, 116.16 (unsubstituted C3(5)), 96.31 (C4).

REFERENCES AND NOTES

- [1] J. P. Freeman and J. J. Gannon, *J. Org. Chem.*, **34**, 194 (1969).
- [2] J. P. Freeman, J. J. Gannon, and D. L. Surbey, *J. Org. Chem.*, **34**, 187 (1969).
- [3] J. F. Hansen and D. E. Vietti, *J. Org. Chem.*, **40**, 816 (1975).
- [4] J. F. Hansen and D. E. Vietti, *J. Org. Chem.*, **41**, 2871 (1976).
- [5] In 1-hydroxypyrazole 2-oxide a situation exists which is similar to that in *N*-unsubstituted pyrazoles, namely that the C3 and C5 positions of the ring are indistinguishable due to the chelation of the acidic proton with both oxygens or to rapid exchange between them. This ambiguity in numbering is indicated by showing the alternative numbering in parentheses, C3(5) or C5(3).

[6] This value is for a sample run in deuteriochloroform, in which **2b** has very limited solubility. Earlier we reported pmr data for **2b** in trifluoroacetic acid (see ref. [4]).

[7] J. P. Freeman and J. F. Hansen, *J. Chem. Soc., Chem. Commun.*, 961 (1972).

[8] G. R. Stevenson, J. F. Hansen, G. Clark, and J. P. Freeman, *J. Org.*

Chem., **44**, 3211 (1979).

[9] J. A. Easter, MS Thesis, Illinois State University, (1988).

[10] A. A. Fadda, *Indian J. Chem.*, **30B**, 749 (1991).

[11] R. J. McConaill and F. L. Scott, *Tetrahedron Letters*, 2993 (1970).

[12] M. Y. Shandala, M. D. Solomon, and E. S. Waight, *J. Chem. Soc.*, 892 (1965).