Nitrone-Azoxy Group Tautomerism. The Structure and Some Reactions of 4-Keto-3,5,5-trimethyl-Δ^2-pyrazoline 2-Oxide[1]

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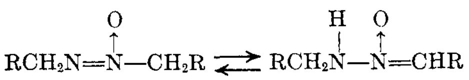
The product obtained by hydrolysis of 4-methoxy-3,5,5-trimethylisopyrazole 2-oxide was shown to be the ketonitrone, 4-keto-3,5,5-trimethyl-Δ^2-pyrazoline 2-oxide. Its reactions with diazomethane, acetic anhydride, and *p*-chlorobenzenediazonium chloride are described. Reduction with potassium borohydride yields an hydroxy azoxy compound which may be re-oxidized to the ketonitrone.

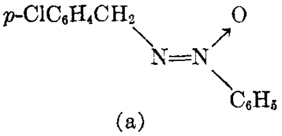
Because little is known about the chemistry of aliphatic azoxy compounds, nothing appears to be known about tautomerism between an azoxy compound and an aminonitrone:



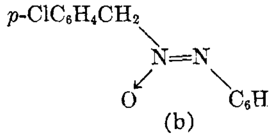
$$RCH_2N{=}\overset{\overset{O}{\uparrow}}{N}{-}CH_2R \rightleftarrows RCH_2\overset{H}{\overset{|}{N}}{-}\overset{\overset{O}{\uparrow}}{N}{=}CHR$$

Such tautomerism is related to that between azo compounds and hydrazones which has been a subject of controversy for many years.[2] The aminonitrones may be regarded as the nitrogen analogs of *aci*-nitro compounds in the same way that azoxy compounds are analogs of nitro compounds.

The acidity of aliphatic azoxy compounds does not seem to compare with that of the corresponding nitro compounds. They cannot be titrated as pseudo-acids and are insoluble in dilute alkali.[3] On the other hand *trans*-azoxy compounds may be isomerized to *cis* isomers by the action of methanolic sodium methoxide and it was proposed that this isomerization occurred through formation of the anion.[4]

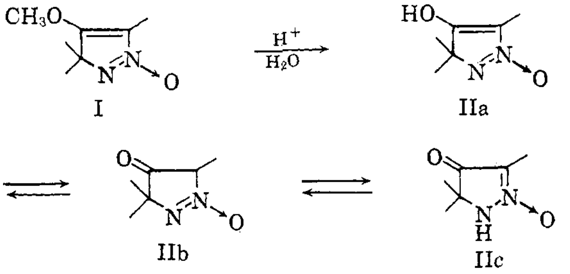


(a)



(b)

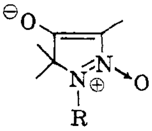
In connection with an interest in this phenomenon and with other studies in the field of aliphatic azoxy compounds, it appeared of interest to examine a compound reported by Fusco and Trisoglio to result from the hydrolysis of 4-methoxy-3,5,5-trimethylisopyrazole 2-oxide (I)[5] since it was supposed to consist of a tautomeric mixture (IIa ⇄ IIb ⇄ IIc).



The evidence for these structures was the lack of reactivity of the compound toward carbonyl reagents, the presence of an acidic hydrogen as evidenced by reaction with alkali and diazomethane, and the formation of coupling products with diazonium salts.

A spectral examination of compound II and some of its derivatives was undertaken to determine their structures. These data are summarized in Table I.

On the basis of these data, structure IIc, 4-keto-3,5,5-trimethyl-Δ^2-pyrazoline 2-oxide, adequately describes Fusco's hydrolysis product. A carbonyl band is clearly present although it is lower than that of ordinary cyclopentanones (1745–1750 cm.$^{-1}$)[6]; this lowering may be ascribed to hydrogen bonding and to interaction with the nitrone group or with the unshared electrons of the amino group. An interaction of the latter type leads to the ionic structure III whose contribution to the ground state of the molecule would account for the lack of reactivity of the carbonyl group of IIc. The corresponding desoxy compound, 3,5,5-trimethyl-4-pyrazolone, also is unreactive toward carbonyl reagents.[7] This contributing structure III is



III. R = H

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[1] This research was carried out under Army Ordnance Contract DA-01-021-ORD-11878.

[2] The status of this problem has recently been summarized: R. O'Connor, *J. Org. Chem.*, **26**, 4375 (1961).

[3] B. W. Langley, B. Lythgoe, and L. S. Rayner, *J. Chem. Soc.*, 4191 (1952).

[4] J. N. Brough, B. Lythgoe, and P. Waterhouse, *ibid.*, 4069 (1954). These authors report the interesting fact that while (a) can be isomerized to its *cis* isomer by base (b) cannot.

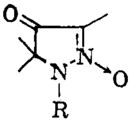
[5] (a) R. Fusco and G. Trisoglio, *Atti accad. Italia, Rend. classe sci. fis. mat. nat.* [7] **2**, 751 (1941); (b) The structure of I has been verified; J .P. Freeman, *J. Org. Chem.*, **27**, 1309 (1962).

[6] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, 2nd ed., p. 132.

[7] R. Fusco and F. D'Alo, *Atti accad. Italia., Rend. classe sci. fis. mat. nat.* [7] **3**, 113 (1942). α-Ketonitrones are known to form 2,4-dinitrophenylhydrazones; V. M. Clark, B. Sklarz, and Sir A. Todd, *J. Chem. Soc.*, 2123 (1959).

TABLE I

SPECTRAL DATA ON 4-KETOPYRAZOLINE 2-OXIDES,

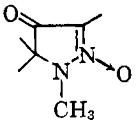


	Infrared (ν cm.$^{-1}$)[a]			Ultraviolet[b]		N.m.r. (τ)[c]		
Compound	$>C{=}O$	$>C{=}\overset{O}{\overset{\uparrow}{N}}$—[d]	R	$\lambda_{max(\mu)}$	ϵ_{max}	$(CH_3)_2C$	CH_3C	R
IIc, R = H—	1730	1588	3200 (bonded OH or NH)	305 244	7,900 8,650	8.55	8.00	2.30
IV, R = CH_3—	1705	1550	. . .	337 247	4,100 9,600	8.73	8.18	7.00
V, R = $CH_3\overset{O}{\overset{\Vert}{C}}$—	1710	1570	1678 ($CH_3\overset{O}{\overset{\Vert}{C}}$—$N<$)	310 244	12,000 8,200	8.38	7.90	7.40

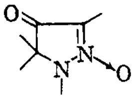
[a] Measured in 0.1-mm. cells on carbon tetrachloride solutions. [b] Measured in ethanol. [c] Measured on a Varian Associates high resolution spectrometer, V-4300 B, using a 40-Mc. probe. Spectra were measured on 10% carbon tetrachloride solutions containing tetramethylsilane as internal reference. [d] Five-membered ring nitrones are reported to absorb strongly between 1570–1620 cm.$^{-1}$; R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir A. Todd, *J. Chem. Soc.*, 2094 (1959).

similar to those suggested to account for the lowered carbonyl reactivity and spectra of β-amino-α,β-unsaturated ketones,[8] lactones, and esters.[9] In all these compounds the conjugated carbonyl structure is favored over an imine structure. In addition near infrared examination of IIc revealed absorption at 1.56 μ which corresponds to the first overtone of an NH vibration.[10] The n.m.r. spectrum of IIc showed only the sharp singlets recorded in Table I and no weak C—H or O—H signals indicative of the presence of IIa or IIb. IIc shows no color with ferric chloride solution.

Methylation of IIc with diazomethane and acetylation with acetic anhydride produced the corresponding N-substituted compounds, IV and V, respectively.



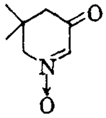
IV



V

The production of compounds IV and V does not prove that in IIc the proton was on nitrogen, but the similarity in the infrared spectra of the three compounds indicates that little change has occurred to the basic system during these reactions. It appears reasonable to assume that a simple replacement of functional groups on nitrogen has occurred.

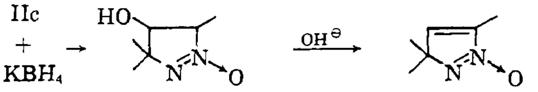
The ultraviolet spectra of compounds IIc, IV, and V also have basic similarities. The low wave length maximum at 244–247 mμ is almost identical in all three compounds. The spectra appear compatible with an excited state such as III, the position of the long wave length maximum being dependent upon the nature of R. An alternative interaction between the nitrone group and the carbonyl group seems less acceptable since the ultraviolet spectrum of ketonitrone VI[11] consists of only one maximum at 280 mμ, ϵ_{max} 17,500.



VI

An independent confirmation of the structure of compound IV was obtained by catalytically reducing it to 1,3,5,5-tetramethylpyrazoline which was produced independently by the methylation of 3,5,5-trimethylpyrazoline.

The reduction of IIc with potassium borohydride proved to be interesting because it indicated the effect of conjugation on the nitrone-azoxy group tautomerism. When the reduction was conducted at 25° for twenty-four hours, a white crystalline solid was obtained. Its infrared spectrum showed that considerable change had occurred. In addition to OH absorption at 3350 cm.$^{-1}$, there was a strong band at 1505 cm.$^{-1}$. Both the carbonyl and nitrone absorption bands of IIc were absent. The 1505-cm.$^{-1}$ band suggested an azoxy linkage[3,12] and structure VII for the reduction product. This structure was confirmed by the conversion of VII to 3,5,5-trimethylisopyrazole 2-oxide (VIII)[5b] with



VII VIII

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[8] N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Am. Chem. Soc.*, **71**, 3337 (1949).

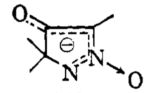
[9] S. A. Glickman and A. C. Cope, *ibid.*, **67**, 1017 (1945); C. A. Grob, *Helv. Chim. Acta*, **33**, 1787 (1950).

[10] W. Kaye, *Spectrochim. Acta*, **6**, 257 (1954). O—H vibrations are found near 1.4 μ and N—H vibrations near 1.5 μ.

[11] R. F. C. Brown, V. M. Clark, and Sir A. Todd, *J. Chem. Soc.*, 2105 (1959).

[12] A range of 1500–1530 cm.$^{-1}$ for the aliphatic azoxy linkage has been reported.[3]

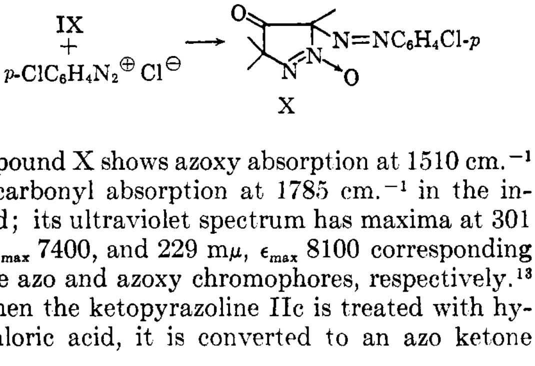
alkali. Compound VIII could be obtained directly from IIc by reduction with potassium borohydride at 75°. Since IIc is acidic and hydrogen is evolved when it is added to the borohydride solution, it is reasonable to assume that it is the enolate IX which is reduced.



IX

The N-aminonitrone grouping in IIc must be stabilized then by the presence of the carbonyl group since it is not regenerated after reduction of this group. That a conjugated structure for IIc is favored is shown by the fact that chromic acid oxidation of alcohol VII regenerates IIc. The nitrone-azoxy group equilibrium must be heavily in favor of the azoxy group and a nitrone structure will only be favored when there is a large increase in resonance energy as in the case of IIc ⟷ III.

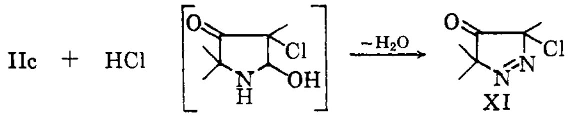
Two other reactions of IIc have been reported: its reaction with diazonium salts and with hydrochloric acid.[5a] Both reactions have been repeated and the proposed structures have been verified. The coupling of *p*-chlorobenzenediazonium chloride with IIc in the presence of sodium acetate must involve enolate IX; based upon infrared evidence coupling occurs as suggested[5a] at position 3:



X

Compound X shows azoxy absorption at 1510 cm.$^{-1}$ and carbonyl absorption at 1785 cm.$^{-1}$ in the infrared; its ultraviolet spectrum has maxima at 301 mμ, ϵ_{max} 7400, and 229 mμ, ϵ_{max} 8100 corresponding to the azo and azoxy chromophores, respectively.[13]

When the ketopyrazoline IIc is treated with hydrochloric acid, it is converted to an azo ketone XI:[5a]



XI

Nitrones are known to react with halogen acids to form hydroxylamines; in this case dehydration may occur to form an azo compound. The structure of 3-chloro-4-keto-3,5,5-trimethylpyrazoline (XI) was established by Fusco,[5a] but its spectral properties were not recorded. Its infrared spectrum shows carbonyl absorption at 1772 cm.$^{-1}$ and a weak band at 1515 cm.$^{-1}$ which may be due to the *cis*-azo function. Its ultraviolet spectrum consisted of three low intensity maxima at 367 mμ, ϵ_{max} 100, 333 mμ, ϵ_{max} 120, and 240 mμ, ϵ_{max} 280.

Summary.—The spectral properties and reactions of the compound obtained by hydrolysis of 4-methoxy-3,5,5-trimethylisopyrazole 2-oxide can be interpreted on the basis of the single structure IIc, 4-keto-3,5,5-trimethyl-Δ²-pyrazoline 2-oxide.

Experimental[14]

4-Keto-1,3,5,5-tetramethyl-Δ²-pyrazoline 2-Oxide. (IV).—A solution of *ca.* 3 g. (0.07 mole) of diazomethane in ether was added dropwise to a solution of 2.8 g. (0.02 mole) of 4-keto-3,5,5-trimethyl-Δ²-pyrazoline 2-oxide[5a] in 75 ml. of absolute ethanol at 20°. A slight exotherm and evolution of gas was noted. The mixture was stirred for an additional 15 min. at room temperature, then cooled in ice and acidified with 5% hydrochloric acid. The resulting solution was diluted with water, the layers separated, and the aqueous layer extracted with three 100-ml. portions of ether. The combined ether extracts were washed with water, dried, and concentrated. Distillation of the remainder yielded a solid, m.p. 43–45°, which proved to be 3-chloro-4-keto-3,5,5-trimethylpyrazoline[5a] produced apparently from the starting ketone during treatment of the reaction mixture with hydrochloric acid.

A second fraction from the distillation, b.p. 65–70° (0.3 mm.), was further purified by vapor chromatography (5-ft. silicone on Chromosorb, 200°) to yield 0.8 g. of 4-keto-1,3,5,5-tetramethyl-Δ²-pyrazoline 2-oxide, b.p. 70–72° (0.3 mm.), n^{20}D 1.4518.

Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.82; H, 7.75; N, 17.94. Found: C, 53.70; H, 7.48; N, 18.06.

Treatment of IV with hydrogen and platinum oxide in a Parr hydrogenator yielded **1,3,5,5-tetramethylpyrazoline,** b.p. 65–68° (30 mm.), n^{20}D 1.4261. This sample had an infrared spectrum which was identical to that of an authentic sample.

1,3,5,5-Tetramethylpyrazoline.—To a mixture of 7.7 g. (0.07 mole) of 3,5,5-trimethylpyrazoline[15] and 3.5 g. of 90% formic acid was added 3.1 ml. of formalin solution. The mixture heated to 60°, turned dark, and evolved gas. After the initial exotherm subsided, the mixture was heated at 90–100° for 12 hr. It was then concentrated and distilled. The first fraction, b.p. 65–70° (30 mm.), was redistilled to yield the desired tetramethylpyrazoline, b.p. 68–70° (30 mm.), n^{20}D 1.4265.

Anal. Calcd. for $C_7H_{14}N_2$: C, 66.62; H, 11.35. Found: C, 66.77; H, 11.27.

1-Acetyl-4-keto-3,5,5-trimethyl-Δ²-pyrazoline 2-Oxide (V).—To 3 g. (0.03 mole) of acetic anhydride was added 2.8 g. (0.02 mole) of IIc. The mixture was warmed for 30 min. on the steam bath to effect solution and allowed to stand overnight at room temperature. Upon cooling the mixture crystallized; the solid was filtered and recrystallized twice from hexane to yield the amide V, m.p. 77–78°.

Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.22; H, 6.86; N, 15.39.

Reduction of 4-Keto-3,5,5-trimethyl-Δ²-pyrazoline 2-Oxide.—A. A mixture of 7.1 g. (0.05 mole) of IIc and 7.1 g. (0.132 mole) of potassium borohydride was stirred in 100 ml. of water overnight. The resulting mixture was saturated with potassium carbonate and continuously extracted with ether for 24 hr. The resulting ether solution was dried and

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[13] Compound X undergoes an hydration reaction upon treatment with wet alcohol[5a]; the structure of this compound has not yet been determined but it appears that a ring opening has occurred.

[14] We are indebted to Mr. R. D. Strahm for the ultraviolet spectral data and near infrared determination. All spectra were measured in ethanol solution. Mrs. Carolyn Haney determined the n.m.r. spectra.

[15] J. Curtius and B Wissing, *J. prakt. Chem.* [2] **50**, 548 (1894).

concentrated to yield a pale yellow oil that distilled at 144° (0.05 mm.). This oil crystallized from cold ether to give platelets of **4-hydroxy-3,5,5-trimethyl-Δ^1-pyrazoline 2-oxide** (VII), m.p. 92–93°.

Anal. Calcd. for $C_6H_{12}N_2O_2$: C, 49.98; H, 8.39; N, 19.43. Found: C, 49.85; H, 8.31; N, 19.75.

The n.m.r. spectrum of VII showed signals at 8.68 τ and 8.60 τ $[(CH_3)_2C]$, at 8.40 τ (doublet, $J = 6$ c.p.s.; CH_3C—H), and a complicated band centering at 5.63 τ which showed a sharp band (*OH*) in the middle of a broad band (*H*C—OH, *H*—C—CH_3). The relative areas of the methyl bands and this unresolved band were 3:1.

B. When the preceding reduction was carried out in the same manner except that the mixture was heated under reflux for 3 hr. instead of stirring at room temperature, the only product obtained was a white solid, m.p. 73–75°, which proved to be identical to 3,5,5-trimethylisopyrazole 2-oxide,[5b] m.p. 77–79°. This same material could also be obtained from VII by heating the latter in ethanolic base for 15 min.

C. Treatment of VII with chromic acid in acetone[16] caused immediate oxidation at room temperature and IIc was isolated by ether extraction of the mixture and identified by infrared analysis and mixed melting point.

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[16] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

Aminonitriles. IV.[1] Preparation and Rearrangement of 3-Substituted 4-Imino-5,5-dimethylimidazolidine-2-thiones

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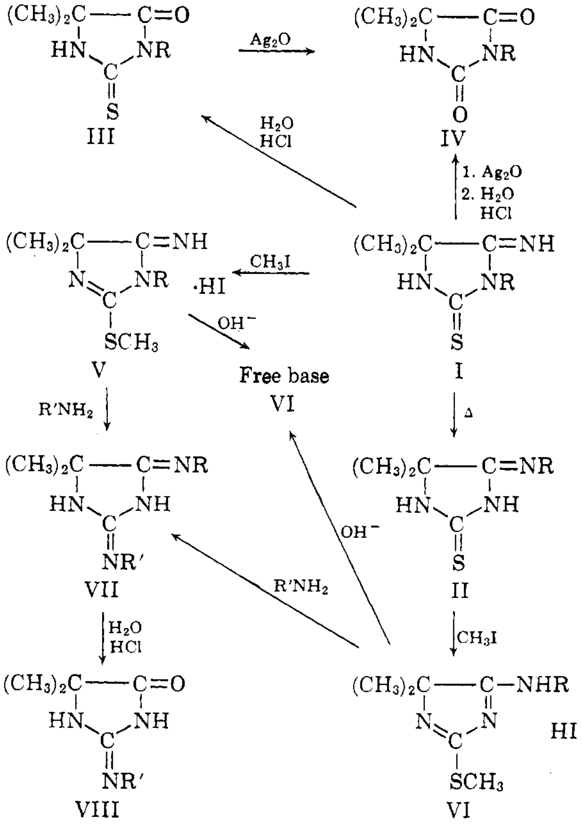
3-Substituted 4-imino-5,5-dimethylimidazolidine-2-thiones, which were prepared by the addition of isothiocyanates to α-aminoisobutyronitrile, rearranged to 4-substituted imino-5,5-dimethylimidazolidine-2-thiones on heating. Methylation of the 3-substituted 4-imino-5,5-dimethylimidazolidine-2-thiones gave the corresponding stable 2-methylmercapto-3-substituted-4-imino 5,5-dimethyl-2-imidazolinium salts. These salts in the presence of base rearranged to 2-methylmercapto-4-substituted amino-5,5-dimethylimidazoles. The 2-methylmercapto-4-substituted amino-5,5-dimethylimidazoles also were obtained directly by the methylation of 4-substituted imino-5,5-dimethylimidazolidine-2-thiones. The positional isomers (V and VI) of the 2-methylmercapto derivatives gave identical 2-substituted imino-4-substituted imino-5,5-dimethylimidazolidines on heating with primary amines.

Previously Cook, *et al.*,[2–4] demonstrated that isothiocyanates combine with α-aminonitriles to give 5-aminothiazoles. They found that the 2-substituted amino-5-aminothiazoles rearranged in the presence of base to 4-substituted 2-mercaptoimidazoles. The isomeric 3-substituted 4-amino-2-mercaptoimidazoles were presumed to be intermediates in this rearrangement. When 2-methylamino-5-aminothiazole was treated with sodium carbonate solution, the rearrangement stopped at this intermediate stage to give 3-methyl-4-amino-2-mercaptoimidazole.[4]

A recent investigation of the reactions of phenyl, benzyl, and 3,4-dichlorobenzyl isothiocyanates with α-aminoisobutyronitrile indicated that the resultant compounds were not the expected thiazoline derivatives. Their infrared spectra showed the presence of one rather than two —C=N— groups. Phenyl isothiocyanate and α-aminoisobutyronitrile in ether at room temperature or in refluxing ether for six hours gave the same compound. This compound was recovered unchanged after refluxing in ethanolic sodium ethoxide solution for one hour. It was hydrolyzed in aqueous hydrochloric acid



R = Phenyl, Benzyl, or 3, 4-Dichlorobenzyl

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[1] Aminonitriles. III. M.-E. Kreling and A. F. McKay, *Can. J. Chem.*, **40**, 143 (1962).

[2] A. H. Cook, J. D. Downer, and I. Heilbron, *J. Chem. Soc.*, 1262 (1948).

[3] C. W. Capp, A. H. Cook, J. D. Downer, and I. Heilbron, *ibid.*, 1340 (1948).

[4] A. H. Cook, J. D. Downer, and I. Heilbron, *ibid.*, 2028 (1948).