Notes

The Reaction between 2,3-Butanedione Monoxime and Aldehyde Oximes. The Preparation of 1-Hydroxyimidazoles 3-Oxides

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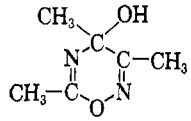
In 1905 Diels and Van der Leeden[1] treated 2,3-butanedione monoxime with aldehyde oximes and obtained products which they postulated as substituted 1,2,5-oxadiazines.[2] For example, 2,3-butanedione monoxime reacted with acetaldoxime to give a product possessing the empirical formula $C_6H_{10}N_2O_2$, to which they assigned



I

the structure of 4-hydroxy-3,4,6-trimethyl-1,2,5-oxadiazine (I). The product was stated to dissolve readily in alkali, a fact that is difficult to rationalize on the basis of the structure assigned.

The product also formed a hydrochloride salt readily. It was stated by these authors[1] that the hydrochloride II could be prepared also by the action of hydrogen chloride on 2,3-butanedione monoxime directly. In this case it was suggested that the first molecule of 2,3-butanedione monoxime was cleaved with hydrogen chloride to acetyl chloride and acetaldoxime. The latter compound then reacted with a second molecule of 2,3-butanedione monoxime in the presence of hydrogen chloride to form the *hydrochloride* II.

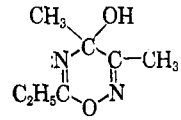
We have repeated both of the reactions indicated above for the preparation of I and its hydrochloride, II.

The product, obtained as a free base, showed a λ_{max}^{EtOH} at 225 mμ (ϵ 5800) in its ultraviolet spectrum. Its infrared absorption spectrum significantly showed no appreciable –OH absorption. An adsorption peak was present at 1235 cm.$^{-1}$, assignable to an N-oxide grouping. The most significant clue to its structure was afforded by its n.m.r. spectrum which showed a sharp singlet at 123 c.p.s. ($CDCl_3$ solvent, A-60) having an area of six protons, assignable to two *identical* methyl groups and a second sharp singlet at 137 c.p.s. having an area of three protons, assignable to the third methyl group.

The hydrochloride salt of the product obtained possessed a similar n.m.r. spectrum with a sharp singlet at 133 c.p.s. with an area of six protons, and a second sharp singlet at 154 c.p.s. with an area of three protons. Its infrared spectrum showed absorptions at 2640 and 2540 cm.$^{-1}$ assignable to a hydrochloride salt, bands at 1645, 1580, and 1495 cm.$^{-1}$ assignable to C=N, and bands at 1210 and 1085 cm.$^{-1}$ assignable to C–O or C–N. The pK_{a1} and pK_{a2} determined[3] were 4.05 and 6.3.

In order to determine whether the two identical methyl groups found as a singlet in the n.m.r. spectra were both derived from the 2,3-butanedione monoxime or whether one was derived from the starting acetaldoxime, the reaction was repeated using propionaldoxime.

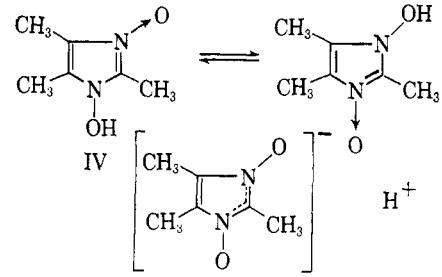
According to the general reaction as postulated by Diels and Van der Leeden,[1] this product should have the structure III.



III

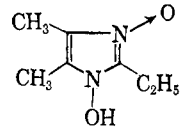
The n.m.r. spectrum of this compound showed the same singlet at 123 c.p.s. with an area of six protons and no methyl absorption in the region of 137 c.p.s. Also present were a triplet centered at 68 c.p.s. attributable to the methyl present in the ethyl group, and a quartet centered at 163 c.p.s. attributable to the methylene group. These data would indicate that the two identical methyl groups must be derived from the methyls of the 2,3-butanedione monoxime.

The structure that would appear to fit best all of these facts is 1-hydroxy-2,4,5-trimethylimidazole 3-oxide (IV). The two methyl groups in the 4- and 5-positions would be identical owing to tautomerism.



IV

The correct structure of the product derived from propionaldoxime would then be 1-hydroxy-2-ethyl-4,5-dimethylimidazole 3-oxide (V).



V

The structure of IV was proved by reduction to 2,4,5-trimethylimidazole with sodium hydrosulfite. The

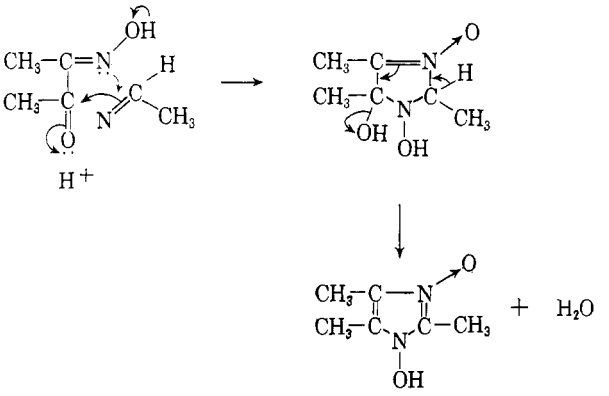
(1) O. Diels and R. Van der Leeden, *Chem. Ber.*, **38**, 3363 (1905).

(2) For a short review of this work, *cf.* Richard H. Wiley, "The Chemistry of Heterocyclic Compounds," Vol. 17, Interscience Publishers, Inc., New York, N. Y., 1962, p. 448.

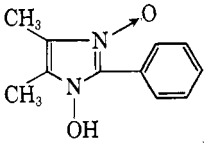
(3) These were determined by titration with potassium hydroxide in dimethylformamide (DMF) and 1:1 DMF-water solutions. Estimation of the pK_a values in water from these data was determined by the method, of D. J. Weber (Meeting of the American Pharmaceutical Association, Miami, Fla. May, 1963).

reduction product showed no depression in melting point when mixed with an authentic sample of 2,4,5-trimethylimidazole and the infrared spectra of the two were identical. The melting point of the hydrochloride of the reduction product showed no depression when mixed with 2,4,5-trimethylimidazole hydrochloride and their infrared spectra were also identical.

A possible mechanism for the formation of these compounds is as follows.



The only examples of 1-hydroxyimidazole 3-oxides in the literature appear in a publication by LaParola.[4] This author investigated the reaction between dimethylglyoxime and benzaldehyde, as well as other aromatic aldehydes, and obtained a substance possessing the formula $C_{11}H_{12}N_2O_2$. To this product he assigned the structure VI. The assignment of structure was based upon the fact that upon reduction with zinc and hydrochloric acid there was obtained 2-phenyl-4,5-dimethylimidazole.[5]



VI

Thus it would appear that 1-hydroxyimidazole 3-oxides can be prepared either by reaction of 2,3-butanedione monoxime with aldehyde oximes or by the reaction of dimethylglyoxime with aldehydes. The first step in these reactions may well be exchange of the oxime grouping between the aldehyde and the α-diketone.

Experimental[6,7]

1-Hydroxy-2,4,5-trimethylimidazole 3-Oxide.—A mixture of 20.0 g. (0.34 mole) of acetaldoxime and 34.2 g. (0.34 mole) of 2,3-butanedione monoxime was warmed to obtain a homogeneous solution. After standing at room temperature for 2 days, the mixture was refluxed 1 hr. and then diluted with 500 ml. of ether. The tan solid removed by filtration weighed 30.42 g. (63%), m.p. 194° dec. Two recrystallizations from 95% ethanol gave material melting constantly at 198° dec.

Anal. Calcd. for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.81; H, 6.87; N, 19.56.

Two grams of the product obtained above was dissolved in chloroform and the hydrochloride precipitated by the addition of an ethereal hydrochloric acid solution. There was obtained 2.14 g. of a tan solid melting at 131.5–133° and showing no depression when mixed with the material prepared by the action of hydrochloric acid on 2,3-butanedione monoxime. The infrared spectra of the two samples were also identical.

1-Hydroxy-2,4,5-trimethylimidazole 3-oxide hydrochloride was prepared in 38% yield by treated 2,3-butanedione monoxime with dry hydrogen chloride according to the procedure for Diels and Van der Leeden.[1] Recrystallization from butanone-2 gave prisms melting at 129.5–131.5°.

Anal. Calcd. for $C_6H_{10}N_2O_2 \cdot HCl$: Cl, 19.85; N, 15.69. Found: Cl, 20.06; N, 15.80.

Reduction of 1-Hydroxy-2,4,5-trimethylimidazole 3-Oxide with Sodium Hydrosulfite.—To 2.84 g. (0.02 mole) of 1-hydroxy-2,4,5-trimethylimidazole 3-oxide in 50 ml. of water was added 17.413 g. (0.1 mole) of sodium hydrosulfite. The mixture was heated under reflux for 3.5 hr. The solution was allowed to cool and was saturated with potassium carbonate and extracted with ether. The ethereal extracts were dried over anhydrous magnesium sulfate, and the ether was removed. There was obtained 0.76 g. of a white solid melting at 131.5–134.5°. Recrystallization from ether gave material melting at 133.5–133.5°. A mixture melting point with authentic 2,4,5-trimethylimidazole[8] (m.p. 134.5 135.5°) showed no depression. Addition of an ethereal hydrogen chloride solution to a solution of the reaction product in ether gave the hydrochloride, melting at 315° and showing no depression when mixed with an authentic sample of 2,4,5-trimethylimidazole hydrochloride (m.p. 314°).

1-Hydroxy-2-ethyl-4,5-dimethylimidazole 3-Oxide.—A mixture of 7.3 g. (0.1 mole) of propionaldoxime and 10.11 g. (0.1 mole) of 2,3-butanedione monoxime was warmed to 40° to obtain a homogeneous solution. After standing overnight, the mixture was refluxed for 3 hr. The viscous oil was triturated with ether and the resulting solid was removed by filtration. There was obtained 10.10 g. (65%) of a cream-colored solid melting at 190.5° dec. Recrystallization from 95% ethanol gave 8.20 g. of colorless prisms melting at 195° dec.

Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94. Found: C, 53.92; H, 7.46; N, 17.82.

(4) G. LaParola, *Gazz. chim. ital.*, **75**, 216 (1945).

(5) Very recently F. Miniscki, *et al.* [*Tetrahedron Letters*, 785 (1963)], described the preparation of 1-hydroxybenzimidazole 3-oxides by the reaction between nitrile oxides and aromatic nitroso derivatives. The properties of these compounds appear to be quite similar to those of 1-hydroxyimidazole 3-oxides; that is, they form a monohydrochloride salt readily, dissolve in aqueous alkali, and are reduced readily to benzimidazoles.

(6) Melting points are corrected.

(7) The author is indebted to Dr. George Slomp and Mr. Forest MacKellar for the n.m.r. spectral studies, to Dr. Gerald Umbreit and his coworkers for the pK_a data and for the microanalytic data, and to Miss Lorraine Pschigoda for infrared spectral studies. He is indebted also to Mr. Albert Lallinger for technical assistance.

(8) R. W. Cowgill and W. M. Clark, *J. Biol. Chem.*, **198**, 36 (1952).

Quinazolines and 1,4-Benzodiazepines. XX.[1] The Formation of 3-Phenylindole-2-carboxaldehydes from 2,3-Dihydro-1*H*-1,4-benzodiazepine 4-Oxides

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Recent interest in nitrones of type I[2] led us to investigate the rearrangement of these compounds with acetic anhydride. The products isolated contained an oxygen function in position 3 of the 1,4-benzodiazepine system. Their structure is in accordance with that postulated for intermediates in the Polonovski reac-

(1) Paper XVIII: L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *J. Org. Chem.*, **29**, 332 (1964); paper XIX: R. I. Fryer, B. Brust, J. Earley, and L. H. Sternbach, *J. Med. Chem.*, **7**, 386 (1964).

(2) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **28**, 2150 (1963); W. Metlesics, G. Silverman, and Leo H. Sternbach, *ibid.*, **28**, 2459 (1963).