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1-Hydroxyxanthine

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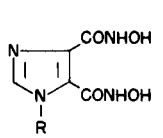
In a previous communication (1), we reported a general synthesis of 1-hydroxy-7-alkylxanthines from the corresponding 1-alkyl-4,5-imidazoledicarbohydroxamic acids (I). Attempts to prepare 4,5-imidazoledicarbohydroxamic acid (I, R=H) at that time failed, but its synthesis has now been realized and its conversion to 1-hydroxyxanthine described below.

The standard reaction of ethyl 4,5-imidazoledicarboxylate with hydroxylamine in ethanol containing sodium ethoxide yielded, after acidification, the half hydroxamic acid ester (II), as was evident from its analysis and n.m.r. spectrum. However, hydroxylamine in pyridine in the presence of potassium hydroxide by the method described recently (2), converted ethyl 4,5-imidazoledicarboxylate to potassium 4,5-imidazolecarbohydroxamate from which I (R=H) was liberated by means of hydrochloric acid.

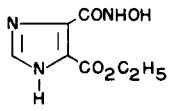
The reaction of the potassium salt of I (R=H) with benzenesulfonyl chloride induced a Lossen-type rearrangement of one of these hydroxamic acid groups to an intermediate isocyanate which cyclized with the neighboring hydroxamic acid group to form 1-hydroxyxanthine which reacted further with the sulfonyl halide present to acylate both the hydroxy group and the imidazole nitrogen atom. Thus, instead of the expected product, 1-benzenesulfonyloxyxanthine (III; R=$C_6H_5SO_2$), there was isolated a dibenzenesulfonyl derivative of 1-hydroxyxanthine, which can be formulated as either the 1-benzenesulfonyloxy-7- or 9-benzenesulfonylxanthine. No attempt was made to establish this structure since it was found that one of the sulfonyl groups was relatively labile. As a matter of fact, when the dibenzenesulfonyl derivative was boiled with ethanol or heated in dimethyl sulfoxide to 95° for 5 minutes, 1-benzenesulfonyloxyxanthine (III; R=$C_6H_5SO_2$) was formed. It is well known that N-acyl imidazoles (hence also purines) are readily converted to the imidazole by nucleophilic reagents attacking the electrophilic acyl center and this premise would be expected to hold in the case under discussion.

Hydrolysis of the dibenzenesulfonyl derivative by aqueous sodium hydroxide furnished the required 1-hydroxyxanthine (III; R=H) whose structure was determined by analysis and spectra. 1-Benzenesulfonyloxy and 1-hydroxyxanthine are arbitarily shown by III, bearing in mind that the labile imidazole hydrogen could reside also at position 7.

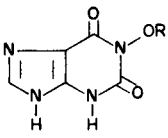
The n.m.r. spectra of some of the compounds described above warrant some comments. A number of these structures possess readily exchangeable protons and attempts to locate these in the n.m.r. spectra in dimethyl sulfoxide -d_6 (35-95°) between 0 and 16.6 δ proved futile. This was particularly noticeable in the xanthine derivatives (III), but in all instances, the addition of deuterium oxide (if solubility permitted) the correct number of exchangeable protons appeared as a broad HOD resonance. Another phenomenon was observed in these compounds. When I (R=H) and II were heated in dimethyl sulfoxide -d_6, the imidazole ring proton resonance moved upfield. This finding was used to locate the imidazole proton at C_8 in 1-benzenesulfonyloxyxanthine (III; R=$C_6H_5SO_2$): The aromatic protons in dimethyl sulfoxide -d_6 at 35° presented themselves as a complex multiplet from which two characteristic sharp spikes stood out at 8.12 and 7.62 δ from tetramethylsilane; at 95°, it was found that only the 8.12 resonance moved upfield by 0.83 δ as monitored on the 7.62 δ and tetramethylsilane resonances, only to return to its original spot on cooling to 35°. Furthermore, the addition of deuterium oxide did not change the behavior of this particular resonance.



I



II



III

EXPERIMENTAL (3)

4(5)Carbethoxy-5(4)imidazolecarbohydroxamic Acid.

A solution of hydroxylamine was prepared by stirring a suspension of dried finely-powdered hydroxylammonium chloride (2.1 g., 0.03 mole) in ice-cold ethanol (50 ml.) with a solution of sodium ethoxide (0.7 g. sodium in 15 ml. ethanol) at room temperature until the solution was neutral to litmus (1 hour). Ethyl 4,5-imidazoledicarboxylate (4.2 g., 0.02 mole) was added to this solution, followed by a solution of sodium ethoxide (0.9 g. of sodium in 20 ml. ethanol) and the mixture allowed to stand at room temperature for 18 hours. Solvents were then removed *in vacuo* and the residual solid (5.5 g.) washed with dry ether (50 ml.) and dried *in vacuo*. The product was obtained by dissolving the salt (2.0 g.) in water (6 ml.) and acidifying the solution with ice-cold concentrated hydrochloric acid to a *p*H of 4. The solid so formed was filtered, washed with ice-cold water (10 ml.) and recrystallized from ethyl acetate or aqueous ethanol. It weighed 1.08 g., (representing a 73% yield from the starting ester), m.p. 188-189°. It gave a purple color with ferric chloride.

The n.m.r. spectrum in $(CD_3)_2SO$ at 35° revealed a triplet at 1.33 and a quartet at 4.35 δ due to the CH_3 and CH_2 of the ester group respectively and a sharp signal at 7.87 δ (imidazole ring proton). Only two signals due to the three exchangeable protons (two of the hydroxamic acid group, one due to the hydrogen on the imidazole

nitrogen) were observed between 0 and 16.6 δ, a very broad flat band centered at 9.45 and a broad but relatively sharp one at 11.5 δ, each representing one proton only. On heating to 90°, the imidazole ring proton appeared now at 7.72 δ. Addition of one drop of D_2O to this hot solution, caused the appearance of a broad band at 3.83 δ which integrated for 3 protons. The infrared spectrum (in Nujol) showed the ester and hydroxamic C=O stretching vibrations at 1695 and 1652 cm^{-1}, respectively.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.21; H, 4.55; N, 21.10. Found: C, 42.31; H, 4.26; N, 21.07.

4,5-Imidazoledicarbohydroxamic Acid.

To a suspension of powdered potassium hydroxide (7.2 g., 0.12 mole) in pyridine (50 ml.) was added ice-cold solution of hydroxylammonium chloride (4.2 g., 0.07 mole) in pyridine (50 ml.). Ethyl 4,5-imidazoledicarboxylate (6.3 g., 0.03 mole) was added and stirring continued for 2.5 hours at 0-5° and then the mixture was set aside for 18 hours at room temperature. Solids were filtered off and dried *in vacuo* (15.5 g.) and used immediately in the experiment described below.

A portion of this mixture of salts (1.0 g.) was dissolved in water (7.0 ml.) and solution cooled at 0-5°, acidified with ice-cold concentrated hydrochloric acid to a *p*H of 3. After standing in an ice-bath for 3 hours, crystals (0.25 g.) were deposited from the solution and were crystallized from 20% aqueous ethanol, m.p. 269-270°. They gave a purple color with ferric chloride.

Its n.m.r. spectrum in $(CD_3)_2SO$ showed the imidazole proton at C_2 as the only signal at 7.85 δ at 35°, which moved to 7.67 δ at 90°. Addition of D_2O to determine exchangeable protons caused precipitation of the product even at 90°.

The infrared spectrum (Nujol) showed two carbonyl bands for this bis-hydroxamic acid, one at 1685, the other at 1645 cm^{-1}.

Anal. Calcd. for $C_5H_6N_4O_4$: C, 32.27; H, 3.25; N, 30.10. Found: C, 32.52; H, 2.94; N, 30.05.

1-Benzenesulfonyloxy-7(or 9)benzenesulfonylxanthine.

A suspension of the salt prepared in the experiment described immediately above, (10 g., consisting of a mixture of potassium 4,5-imidazoledicarbohydroxamate and potassium chloride) was stirred in tetrahydrofuran (100 ml.) while a solution of benzenesulfonyl chloride (8 ml.) in tetrahydrofuran (30 ml.) was added at a rate so as to maintain the temperature between 20-22° (0.25 hour). The mixture was stirred 0.5 hour longer, then sodium acetate trihydrate (4.0 g.) was added and stirring continued for 2 hours. Solids were filtered off and washed with tetrahydrofuran (three 40 ml. portions). Tetrahydrofuran was removed *in vacuo* (below 40°) and the residue partitioned between water (150 ml.) and petroleum ether (b.p. 30-60°, 75 ml.). The solid which separated was filtered and washed with cold ethanol (20 ml.) and recrystallized from ethanol, m.p. 215-217°. It weighed 0.45 g. (9% based on the starting ester).

The n.m.r. spectrum in $(CD_3)_2SO$ at 35° showed the proton at C_8 as a relatively sharp band at 8.83 δ and the benzenenoid protons as a complex pattern, center of gravity at 7.62 δ. On heating to 95°, the downfield proton vanished and the aromatic proton pattern changed. On cooling to 35°, this pattern persisted. Dilution of the contents of the n.m.r. tube with water afforded a solid whose melting point and mixed melting points and infrared spectrum were identical to 1-benzenesulfonyloxyxanthine, described below.

Its infrared spectrum (Nujol) showed two carbonyl bands at 1755 and 1710 cm^{-1}.

Anal. Calcd. for $C_{17}H_{12}N_4O_7S_2$: C, 45.51; H, 2.69; N, 12.49. Found: C, 45.84; H, 2.57; N, 12.47.

1-Benzenesulfonyloxyxanthine.

The bis-benzenesulfonyl derivative (0.4 g.) prepared above was boiled with ethanol (200 ml.) for 0.5 hour and the solution set aside at 25° for some time (4-7 days). The product (0.17 g., 61%) crystallized out as yellow needles, m.p. 235-236°.

The n.m.r. spectrum in $(CD_3)_2SO$ at 35° revealed a complex multiplet between 7.55 and 8.32 and a broad flat signal at 12.5 δ in the ratio of 7:1 and these represent the benzenenoid, the purine proton at C_8 and probably the exchangeable proton on the imidazole ring, the downfield proton being the one of the -CONH- portion of the pyrimidine system. On heating to 90°, one of the bands in the complex multiplet moved (as described above) and the broad band flattened out even more and its center moved to 10.7 δ. Addition of two drops of D_2O to the solution at 95° caused HOD resonances to appear as a broad but relatively sharp band at 4.45 δ which represented 2 protons when compared to 5 protons in the complex multiplet.

The infrared spectrum (Nujol) showed the C=O bands 1740 and 1700 cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_4O_5S$: C, 42.87; H, 2.62; N, 18.18. Found: C, 43.00; H, 2.57; N, 18.10.

1-Hydroxyxanthine.

1-Benzenesulfonyloxy-7(or 9)benzenesulfonylxanthine (0.44 g., 0.001 mole) was boiled with 5% aqueous sodium hydroxide (8 ml.) until a clear solution was obtained (1-2 minutes). After cooling the solution was acidified with cold hydrochloric acid. On keeping in an ice-water bath for 3 hours, the product precipitated. It was crystallized from water, (0.14 g., 83%), and was dried at 130° before analysis. On being heated, it decomposed at high temperature, turning dark, but did not melt by 480°. U. V.: λ max (H_2O) 266 (log ε, 4.02); (0.01 NaOH) 284 (log ε, 3.96).

The n.m.r. spectrum in $(CD_3)_2SO$ at 50° showed the resonance to the proton at position 8 as a sharp band at 7.97 δ. Addition of D_2O caused precipitation of the product.

Its infrared spectrum (Nujol) showed C=O absorption as a strong band at 1730 and as a very strong band at 1690 cm^{-1}.

Anal. Calcd. for $C_5H_4N_4O_3$: C, 35.72; H, 2.40; N, 33.33. Found: C, 35.97; H, 2.39; N, 33.47.

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REFERENCES

(1) L. Bauer, C. N. V. Nambury and D. Dhawan, *J. Heterocyclic Chem.*, 1, 275 (1964).

(2) G. B. Backman and J. E. Goldmacher, *J. Org. Chem.*, 29, 2576 (1964).

(3) Melting points were determined on a Mel-Temp apparatus, Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland, Micro-Tech Laboratories, Inc., Skokie, Illinois and those for nitrogen by Mr. Leo Horner, using the Coleman Nitrogen Analyzer, Model 29. Nuclear magnetic resonance (n.m.r.) spectra were determined on a Varian A-60 spectrometer using tetramethylsilane (TMS) as internal standard and resonances are reported in parts per million (δ) downfield from TMS from 0 to 16.6 δ. Infrared spectra were recorded on the Perkin Elmer 337 spectrophotometer and ultraviolet spectra on the Beckman DK-1 recording spectrophotometer.

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