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Synthesis of 1-Hydroxyxanthines (1)

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The synthesis of 1-hydroxy-7-alkylxanthines from the corresponding diethyl 1-alkyl-4,5-imidazoledicarboxylates by means of a modified Lossen rearrangement is described. The products were characterized by their spectra and identified by hydrolysis with concentrated hydrochloric acid at elevated temperatures to the corresponding N-alkyl-substituted glycines.

The facile transformation of diethyl succinate to 3-benzenesulfonyloxy-3-hydroxy-5,6-dihydrouracil (2) paved the way for the ready conversion of a 1,4-dicarboxylic acid to derivatives of N-hydroxyuracil. This method was then applied to the synthesis of 3-hydroxy-2,4-quinazolinedione (3) from diethyl phthalate (4, 5) which represents a facile route to attach an N-hydroxyuracil moiety to an aromatic ring. This approach was studied with the intent to fuse such an N-hydroxyuracil fragment to an imidazole ring to furnish 1-hydroxyxanthines (3). The starting materials chosen for such a synthesis were the diethyl 1-alkyl-4,5-imidazoledicarboxylates (I), and this is described in detail when R=CH_3, R'=H. When diethyl 1-methyl-4,5-imidazoledicarboxylate was treated with hydroxylamine and sodium ethoxide, the hydroxamate (II) was isolated and used immediately in the next step. Addition of benzenesulfonyl chloride to a suspension of II in tetrahydrofuran brought about a vigorous reaction which yielded a crystalline product whose analysis and spectra could be accommodated by either the 7- or 9-methyl-1-benzenesulfonyloxyxanthine structure III and IIIa, respectively. Hydrolysis of the sulfonyl ester so isolated produced a 1-hydroxyxanthine, which could be a 1-hydroxy 7- or 9-alkylxanthine, IV or V (R = CH_3; R' = H).

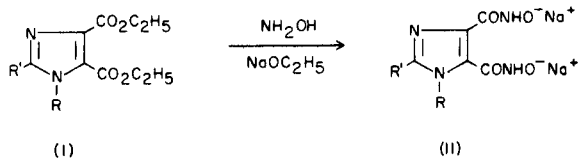
Both 1-hydroxyxanthine structures are plausible products and could arise if either the 4 or 5-carbohydroxamate in II was degraded during this Lossen type of rearrangement. Comparison of the spectral characteristics of the unknown 7- or 9-methyl-1-hydroxyxanthine with those of the known 7- and 9-methylxanthine (Table I) did not help to decide on the unequivocal assignment of the structure. Perhaps this was not surprising since IV and V possess almost identical electronic environments and the difference might be too subtle to impart large differences to the absorption spectra. In the nuclear magnetic resonance (n.m.r.) spectra of III and IV, the N-methyl resonances show up with about the same chemical shift as that of 7-methylxanthine. However, more positive proof of structure was sought. Attempts to reduce the product catalytically to the known 7- or 9-methylxanthines under a variety of conditions proved unsuccessful. Ultimate proof of structure was provided when the 1-hydroxyxanthine was hydrolyzed with concentrated hydrochloric acid at 220°.

It had been shown previously that 7-methylxanthine (6) was hydrolyzed to sarcosine. To rule out alkyl migration of the alkyl group at the 7- or 9-nitrogen atoms, 9-methylxanthine was hydrolyzed under similarly drastic conditions and gave rise only to glycine. When the unknown 1-hydroxy 7- or 9-methylxanthine was subjected to such a hydrolysis, sarcosine was isolated by paper chromatography. It was identified by its infrared and n.m.r. spectra. Thus the structure of the unknown was shown to be IV, R = CH_3; R' = H, the sarcosine skeleton arising from the atoms of IV which are encircled.

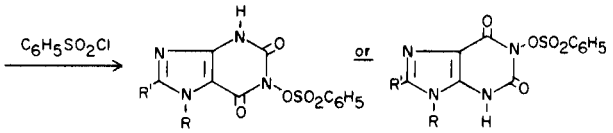
The synthesis was then extended to 1-hydroxy-7-benzylxanthine (IV; R = $C_6H_5CH_2$; R' = H) from diethyl 1-benzyl-4,5-imidazoledicarboxylate (I; R = $C_6H_5CH_2$; R' = H) by a route similar to that used for the methyl analog. The product on drastic hydrolysis with concentrated hydrochloric acid led to N-benzylglycine which was identified by comparison with an authentic specimen by means of paper chromatography. The reaction sequence was also applied to the conversion of diethyl 1-methyl- and 1-benzyl-2-methylmercapto-4,5-imidazoledicarboxylates (I; R = CH_3 or $C_6H_5CH_2$; R'' = CH_3S) to the corresponding 1-hydroxy-7-alkyl-8-methylmercaptoxanthines (IV), where R = CH_3 and $C_6H_5CH_2$ and R' = CH_3S, respectively. Their structures were proved again by degradation to the corresponding N-substituted glycines.

The isolation of 1-hydroxy-7-alkylxanthines (IV) means that the 4-hydroxamate group of II was degraded during the reaction with sulfonyl halide. To explain such a preferential reaction it might be argued that the 4-hydroxamate anion is less hindered than that at position 5 and thus more prone to react initially with the electrophilic sulfur of the sulfonyl chloride to form the sulfonic ester. The 4-hydroxamate group might also be expected to rearrange in preference to that at 5 on the basis of Schechter's recent observation (7) that the Lossen rearrangement proceeded faster as the electron-donating properties of the migrating group was increased. In the reaction under study, the 4 position of the imidazole ring presents a potentially more nucleophilic site than the 5 position (8).

This sequence of reactions (I to IV) failed under the conditions so developed when diethyl 4,5-imidazoledicarboxylate (I; R = R' = H) and diethyl 1-methyl-2-mercapto-4,5-imidazoledicarboxylate (I; R = CH_3; R' = SH) were the starting esters. No explanation can be offered at present. The only feature common to both starting esters is the presence of a relatively acidic hydrogen in each, *viz.*, the imidazole NH and thiol SH respectively.



(I) (II)



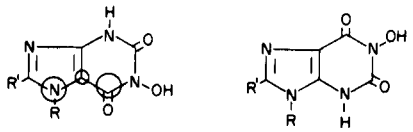
(III) (IIIa)

EXPERIMENTAL (9)

Diethyl 4,5-Imidazoledicarboxylate.

A slow stream of dry hydrogen chloride was led through a suspension of 4,5-imidazoledicarboxylic acid (10) (5 g., 0.03 mole) in boiling ethanol (200 ml.) until a solution was obtained (4.5 hours). The solution was concentrated at 30 mm. to 25 ml. and the residue poured into saturated sodium bicarbonate solution (45 ml. or until the *p*H was 9). Extraction with chloroform (three 50 ml. portions) gave the ester (4.8 g., 71%) which crystallized from benzene, m.p. 149-150°, lit. (11) m.p. 151-152°.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.19. Found: C, 51.05; H, 5.68; N, 13.13.



(IV) (V)

TABLE I

Spectral Data of 1-Hydroxyxanthines and Model Compounds

Compound	Infrared Absorption Bands (Nujol) 1800-1500 cm^{-1}	Ultraviolet Spectrum λ max in mμ (log ε max) Water	0.01N NaOH	N.m.r. resonances in CF_3CO_2H δ in p.p.m. from Tetramethylsilane (S-CH_3)	(N-CH_3)	(N-CH_2)	(H at C_8)
1-Benzenesulfonyloxy-7-methylxanthine	1740s, 1700s, 1600m 1580m, 1500vw	271(3.92) 269(3.94) (d)	292(3.96) 288(4.02) (e)	-	4.33	-	8.91
1-Hydroxy-7-methylxanthine	1740s, 1700s, 1590w 1580w, 1505w	268(4.01)	283(3.97)	-	4.38	-	9.00
7-Methylxanthine (a)	1730sh, 1680vs-b (f) 1570m, 1500vw	268(4.00) Lit. (b) 268(4.01)	288(3.92) 287(3.93) 231(3.67)	-	4.41	-	9.00
9-Methylxanthine (c)	1730sh, 1705vs-b 1570w	264(4.01) 237(3.92) Lit. (b) 265(4.01) 234(3.92)	278(3.97) 244(3.98) 277(3.97) 245(3.98)	-	4.16	-	9.03
1-Benzenesulfonyloxy-7-benzylxanthine	1750m, 1705s-b 1605w, 1575m, 1560w 1500w	266(4.12) (d)	283(4.25) (e)	-	-	5.75	8.80
1-Hydroxy-7-benzylxanthine	1740sh, 1715s, 1670s-b 1600vw, 1570m, 1505m	268(4.22) (d)	287(4.29) (e)	-	-	5.81	8.86
1-Benzenesulfonyloxy-7-methyl-8-methylmercaptoxanthine	1760s, 1740s, 1720s 1700s, 1610w, 1600vw 1565m-b	292(4.31) (d)	302(4.35) (e)	2.89	4.05	-	-
1-Hydroxy-7-methyl-8-methylmercaptoxanthine	1700sh, 1675vs-b 1650sh, 1640sh	288(4.03) (d)	303(3.85) (e)	2.91	4.08	-	-
1-Benzenesulfonyloxy-7-benzyl-8-methylmercaptoxanthine	1755s, 1710s-b 1600m, 1555m	292(4.26) (d)	301(4.33) (e)	2.95	-	5.70	-
1-Hydroxy-7-benzyl-8-methylmercaptoxanthine	1740m-b, 1660s-b 1575w	290(4.44) (d)	304(4.23) (e)	2.83	-	5.53	-

(a) Prepared by the method of J. Sarasine and E. Wegmann, *Helv. chim. acta*, 7, 713 (1924). (b) W. Pfleiderer and G. Nübel, *Ann.*, 647, 155 (1961). (c) Synthesized according to the procedure of H. C. Koppel and R. K. Robins, *J. Am. Chem. Soc.*, 80, 2751 (1958). (d) Measured in ethanol. (e) Measured in 0.01N NaOH in 90% ethanol. (f) b after vs, s or m means broad band.

Diethyl 1-Methyl-4,5-imidazoledicarboxylate.

A solution of diethyl 4,5-imidazoledicarboxylate (5.4 g., 0.02 mole) in ethanol (200 ml.) containing sodium ethoxide (0.6 g. of sodium) was treated with methyl iodide (2.1 ml., 0.03 mole) and heated under reflux for 4 hours. Solvents were then removed *in vacuo* and the residue treated with 5% sodium carbonate and the product extracted into chloroform. Distillation furnished the ester (3.8 g., 70%), b.p. 148-150° at 0.25 mm.

Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.10; H, 6.19; N, 12.38. Found: C, 53.32; H, 6.16; N, 12.26.

Diethyl 1-Benzyl-4,5-imidazoledicarboxylate.

A solution of diethyl 4,5-imidazoledicarboxylate (6.3 g., 0.03 mole) in ethanol (300 ml.) containing sodium ethoxide (0.9 g. of sodium) was treated with benzyl chloride (7.6 g., 0.06 mole) and heated under reflux for 3 hours. Solvents were then removed *in vacuo* and the residue treated with 5% sodium carbonate (50 ml.) and the product extracted with chloroform. Distillation gave the ester (6.1 g., 88%), b.p. 200-202° at 0.1 mm.

Anal. Calcd. for $C_{16}H_{18}N_2O_4$: N, 9.27. Found: N, 9.55.

Diethyl 1-Methyl-2-mercapto-4,5-imidazoledicarboxylate.

This product was obtained by the method of Jones (11) in 70% yield starting from ethyl N-formyl sarcosine. It crystallized from ethyl acetate-hexane in colorless needles, m.p. 126-127°. Its n.m.r. spectrum (in $CDCl_3$) showed resonances for the CH_3 of the ester at 1.42 (triplet), the CH_2 of the esters as two overlapping quartets at 4.50, the N-CH_3 at 3.78 (singlet) and SH as a broad band at 12.30 ppm., from tetramethylsilane.

Anal. Calcd. for $C_{10}H_{14}N_2O_4S$: N, 10.85. Found: N, 10.60.

Diethyl 1-Methyl-2-methylmercapto-4,5-imidazoledicarboxylate.

A solution of diethyl 1-methyl-2-mercapto-4,5-imidazoledicarboxylate (7.74 g., 0.03 mole) in anhydrous acetone (75 ml.) containing methyl iodide (13.8 g., 0.1 mole) and anhydrous potassium carbonate (2.7 g., 0.03 mole) was warmed under reflux for 3 hours. Solvents were then removed *in vacuo*, and the residual gum triturated with 10% sodium carbonate solution (50 ml.) and the oil extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4) and distilled to give the ester, (6.44 g., 79%), b.p. 160-165° at 0.2 mm.

Anal. Calcd. for $C_{11}H_{16}N_2O_4S$: N, 10.29. Found: N, 10.22.

Diethyl 1-Benzyl-2-methylmercapto-4,5-imidazoledicarboxylate.

This was made in 76% yield from diethyl 1-benzyl-2-mercapto-4,5-imidazoledicarboxylate (12) in a manner analogous to that described above for the 1-methyl compound. After the addition of 10% sodium carbonate solution, a solid was obtained which crystallized from cyclohexane to furnish colorless rhombs, m.p. 72-73°.

Anal. Calcd. for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.78; N, 8.04. Found: C, 58.67; H, 5.79; N, 8.19.

1-Benzenesulfonyloxy-7-methylxanthine.

A solution of hydroxylamine in ethanol was prepared by stirring powdered, dried hydroxylammonium chloride (1.54 g., 0.022 mole) with sodium ethoxide (from 0.51 g. of sodium in 40 ml. of ethanol) at room temperature until double decomposition had taken place (neutral to litmus) (two hours required). This solution was chilled to 5° and then there was added diethyl 1-methyl-4,5-imidazoledicarboxylate (2.3 g., 0.01 mole), followed in 10 minutes by an ethanolic solution of sodium ethoxide (from 0.46 g. of sodium in 20 ml. of ethanol). The mixture was stirred at room temperature (4 hours) and the sodium hydroxamate filtered, washed with dry ether (50 ml.) and dried *in vacuo*. The salts gave a violet color with ferric chloride solution.

The above product was suspended in tetrahydrofuran (30 ml.) and stirred while benzenesulfonyl chloride (2.5 ml., 0.04 mole) in 25 ml. tetrahydrofuran was added over 10 minutes. The rate of addition was controlled in order to maintain the temperature between 20-23° (13). After 0.5 hour, sodium acetate trihydrate (2.0 g.) was added and the mixture stirred 1 hour longer. Solids were then filtered and the precipitate washed with tetrahydrofuran (three 30 ml. portions). The tetrahydrofuran solution was evaporated *in vacuo* (below 40°) and the residue triturated with water (50 ml.) and petroleum ether, b.p. 30-60°, (20 ml.). The solid separating at the interface was filtered and crystallized from ethanol. Colorless needles, 0.4 g. (17% based on the ester), m.p. 232-233° dec., were obtained.

Anal. Calcd. for $C_{12}H_{10}N_4O_5S$: C, 44.74; H, 3.12; N, 17.38. Found: C, 44.92; H, 3.33; N, 17.29.

1-Hydroxy-7-Methylxanthine.

1-Benzenesulfonyloxy-7-methylxanthine (0.4 g., 0.0013 mole) was boiled with 10% sodium hydroxide solution (5 ml.) until a clear solution was obtained (1 to 2 minutes). The solution was cooled and acidified with hydrochloric acid. The product precipitated after standing several hours in an ice bath. It was recrystallized from water, (0.182 g., 78%), m.p. 339° dec.

Anal. Calcd. for $C_6H_6N_4O_3$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.31; H, 3.62; N, 30.60.

This product (0.08 g.) was heated with concentrated hydrochloric acid (10 ml.) at 220° for 6 hours. The solvents were removed and the residue examined in the following manner: Its n.m.r. spectrum in D_2O showed signals at δ = 4.25 (CH_2) and 3.08 (NCH_3) from T.P.S. (14); comparable to those shown by authentic sarcosine hydrochloride in D_2O. A solution of the residue in base (20% NaOH pellets) in D_2O showed signals at δ = 3.58 (CH_2) and 2.75 (NCH_3) from T.P.S., similar to those shown by sarcosine in the same solvent. When the basic solution of the unknown was acidified with hydrochloric acid and evaporated to dryness, the infrared spectrum (Nujol) was superimposable upon that of sarcosine hydrochloride. Sarcosine was also identified by paper chromatography by the method of Weissmann (6).

1-Benzenesulfonyloxy-7-benzylxanthine.

The synthesis was achieved from diethyl 1-benzyl-4,5-imidazoledicarboxylate (2.9 g., 0.01 mole) essentially as described above for the methyl analog. The sodium hydroxamate did not precipitate and was isolated by evaporation of the ethanol *in vacuo* after 20 hours. Rearrangement of the sodium hydroxamate with benzenesulfonyl chloride at 20-23° as described above furnished the product (1.3 g., 49% yield based on the ester), which crystallized from ethanol, m.p. 225-226°.

Anal. Calcd. for $C_{18}H_{14}N_4O_5S$: C, 54.26; H, 3.54; N, 14.06. Found: C, 54.37; H, 3.81; N, 14.01.

1-Hydroxy-7-benzylxanthine.

1-Benzenesulfonyloxy-7-benzylxanthine (1.0 g.) was boiled with 5% sodium hydroxide solution (10 ml.) until a clear solution was obtained (1 to 2 minutes). The solution was cooled and acidified with hydrochloric acid. The product precipitated after standing 4 hours in an ice-water bath. It was crystallized from water, (0.55 g., 84%), m.p. 273-274°.

Anal. Calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.88; N, 21.70. Found: C, 55.67; H, 4.13; N, 21.55.

When 10% sodium hydroxide solution was used for the hydrolysis, a lower yield was obtained. Hydrolysis of this product with concentrated hydrochloric acid at 180° for six hours gave only N-benzylglycine, identified by comparison with an authentic sample by means of paper chromatography using the solvents indicated by Weissmann (6).

1-Benzenesulfonyloxy-7-methyl-8-methylmercaptoxanthine.

This was made from diethyl 1-methyl-2-methylmercapto-4,5-imidazoledicarboxylate (5.44 g., 0.02 mole) in a manner virtually identical to that described for 1-benzenesulfonyloxy-7-methylxanthine with the following modification: the ester was allowed to stand with hydroxylamine and sodium ethoxide for 18 hours and the solvents evaporated *in vacuo*, then the residual solid was washed repeatedly with hexane and dried. The crude hydroxamate was treated with benzenesulfonyl chloride as described. The product (1.25 g., 17%) crystallized from tetrahydrofuran-hexane, m.p. 221-222°.

Anal. Calcd. for $C_{13}H_{12}N_4O_5S_2$: C, 42.38; H, 3.28; N, 15.21; S, 17.40. Found: C, 42.58; H, 3.40; N, 15.20; S, 17.37.

1-Hydroxy-7-methyl-8-methylmercaptoxanthine.

The benzenesulfonyl derivative (2.29 g., 0.007 mole) was dissolved in boiling 10% sodium hydroxide solution (30 ml., 2 minutes). The solution was cooled and acidified with hydrochloric acid. The product precipitated after standing several hours in an ice-water bath. It was crystallized from water (1.2 g., 91%) m.p. 295° dec. The product was dried at 90° *in vacuo* prior to analysis.

Anal. Calcd. for $C_7H_8N_4O_3S \cdot H_2O$: C, 34.15; H, 4.06; N, 22.51. Found: C, 34.58; H, 4.02; N, 22.96.

The water of crystallization was removed by either heating at 150° or by azeotropic distillation with benzene.

Anal. Calcd. for $C_7H_8N_4O_3S$: C, 36.85; H, 3.53; N, 24.55. Found: C, 36.69; H, 3.71; N, 24.35.

Hydrolysis at 220° with concentrated hydrochloric acid gave sarcosine, identified as above.

1-Benzenesulfonyloxy-7-benzyl-8-methylmercaptoxanthine.

This was prepared as described in full for the 7-methyl analog from diethyl 1-benzyl-2-methylmercapto-4,5-imidazoledicarboxylate (3.28 g., 0.01 mole). The product (0.95 g., 46% yield) crystallized from ethanol, m.p. 220-222° dec.

Anal. Calcd. for $C_{19}H_{16}N_4O_5S_2$: C, 51.34; H, 3.62; N, 12.60; S, 14.43. Found: C, 51.57; H, 3.76; N, 12.68; S, 14.34.

1-Hydroxy-7-benzyl-8-methylmercaptoxanthine.

Hydrolysis of the benzenesulfonyl derivative (0.44 g., 0.001 mole) was carried out in a manner similar to the methyl analog to yield the

product (0.085 g., 28%) m.p. 269-270° (from ethanol).

Anal. Calcd. for $C_{13}H_{12}N_4O_3S$: C, 51.30; H, 3.97; N, 18.41; S, 10.53. Found: C, 51.44; H, 4.22; N, 18.08; S, 10.66.

The compound gave a red solution with aqueous ferric chloride solution. Hydrolysis as before with concentrated hydrochloric acid at 180° only led to N-benzylglycine.

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(8) For example, nitration occurs preferentially at the 4 position, see K. Hofmann, "Imidazole and its Derivatives, Part I", Interscience Publishers, Inc., New York, N. Y., 1953, p. 127.

(9) All boiling and melting points are uncorrected. Melting points were determined on a Mel-Temp apparatus. Analyses were performed by Dr. Kurt Eder, Geneva, Switzerland and Micro-Tech Laboratories, Inc., Skokie, Illinois. Ultraviolet spectra were measured on a Beckmann DK-1 recording spectrophotometer. Infrared spectra were obtained using a Beckman IR-4 and a Perkin Elmer Model 337 recording spectrophotometers. The Varian A-60 spectrometer was used to produce the nuclear magnetic resonance spectra.

(10) Purchased from Aldrich Chemical Co., Milwaukee, Wisconsin.

(11) R. G. Jones, *J. Am. Chem. Soc.*, 74, 1085 (1952), synthesized this ester from the nitric acid oxidation of diethyl 2-mercapto-4, 5-imidazoledicarboxylate.

(12) J. A. Carbon, *J. Am. Chem. Soc.*, 80, 6083 (1958).

(13) The yield of the product is decreased considerably if the temperature is permitted to rise above 25°.

(14) Sodium 3-(trimethylsilyl)-1-propanesulfonate.

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