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### 3-Hydroxylumazine

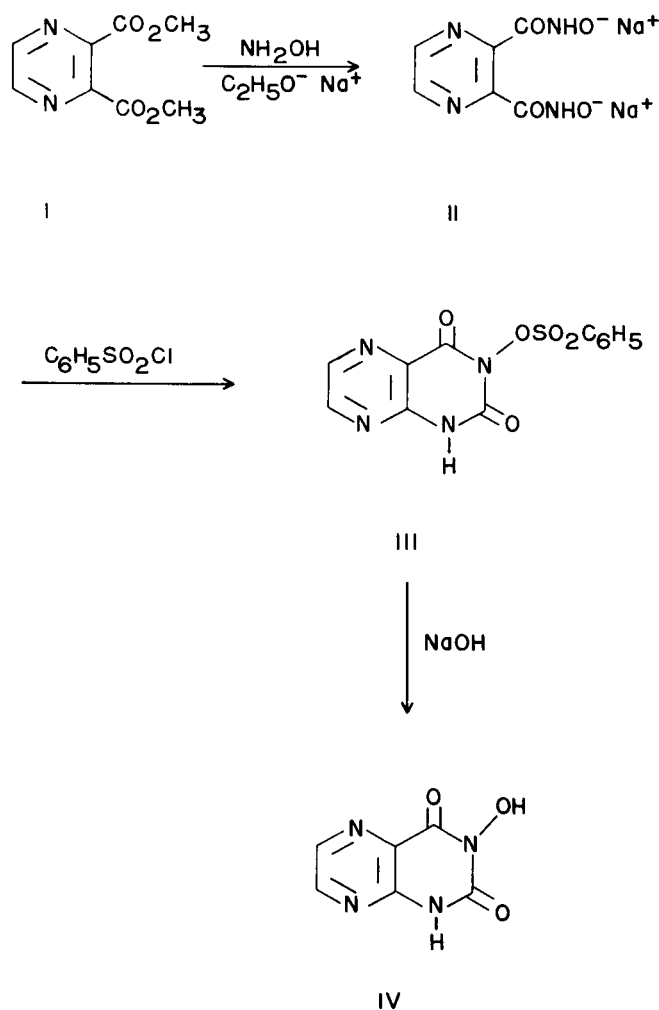
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In our continuing interest in the synthesis of condensed *N*-hydroxyuracils, we turned our attention to the lumazine system. This paper describes a convenient synthesis of 3-hydroxylumazine; and while this work was in progress, there appeared syntheses of several related *N*-oxidized pteridine derivatives, specifically, that of 1-hydroxy-6,7-dimethylumazine (1) and of some lumazine 5-oxides (2).

The synthesis which is described followed the pattern established for the transformation of *vic.* aromatic dicarboxylic acids via their bis hydroxamic acids to the condensed *N*-hydroxyuracils (3). 2,3-Pyrazinedicarboxylic acid was chosen as starting material and was converted to its methyl ester (I), which in turn readily reacted with hydroxylamine and sodium ethoxide to furnish the sodium hydroxamate (II). Treatment of II with benzenesulfonyl chloride brought about the degradation of one of the hydroxamic acid groups to an isocyanate which cyclized with the other hydroxamic acid group to produce, after acylation, 3-benzenesulfonyloxylumazine (III). Short exposure of III to hot dilute aqueous sodium hydroxide solution yielded 3-hydroxylumazine (IV).

Although 3-hydroxylumazine represents a potentially tautomeric system, spectral evidence is in favor of the diketo form (IV).

This conclusion was reached by examining first the infra-red spectra of the corresponding sulfonyl ester (III) and other model compounds. 3-Benzene-sulfonyloxylumazine (III) in Nujol showed two strong carbonyl bands at 1770 and 1748  $\text{cm}^{-1}$ , the next band in that region being a medium one at 1570  $\text{cm}^{-1}$ . However, the infrared spectrum of 3-hydroxylumazine (IV) (in Nujol) showed a weak but relatively sharp band at 3550  $\text{cm}^{-1}$  (free OH stretching mode), a medium broad band at 3350  $\text{cm}^{-1}$  (bonded OH, NH) and the two carbonyl groups at 1730 (strong) and 1670 (strong and broad)  $\text{cm}^{-1}$ . That the carbonyl stretching frequencies in III appeared at higher frequencies than in IV is understandable when one considers that the strongly electron-attracting benzenesulfonyl group would tend to impart considerably more electrophilic character to the carbonyl carbons and in effect would tend to shorten the carbon-oxygen bond. This phenomenon has been observed in a number of related compounds (4).



#### EXPERIMENTAL

Melting points are uncorrected. Analyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Infrared and ultra-violet spectra were determined on the Perkin-Elmer 337 and on the Beckman DK-1 spectrophotometers, respectively. N.m.r. spectra were recorded at 60 Mc. by means of the Varian A-60 spectrometer, all signals being recorded in p.p.m. ( $\delta$ ) downfield from tetramethylsilane (TMS) as the internal standard.

## 3-Benzenesulfonyloxylumazine (III).

A solution of hydroxylammonium chloride (9.24 g., 0.7 mole) in absolute ethanol (150 ml.) was neutralized by sodium ethoxide solution (3 g. of sodium in 60 ml. of ethanol) and then filtered to remove salt. A solution of methyl 2,3-pyrazinedicarboxylate (5) (11.76 g., 0.06 mole) in ethanol (50 ml.) was added dropwise to a stirred ethanolic solution of hydroxylamine at 0-5°, followed by the addition of sodium ethoxide (3.0 g. of sodium in 60 ml. ethanol). The reaction mixture was then allowed to stand at room temperature for 18 hours. Petroleum ether (b.p. 30-60°, 150 ml.) was added to this mixture and the gelatinous yellow solid (II) was filtered and washed several times with dry ether and dried *in vacuo* (18 hours, over sulfuric acid).

To a stirred suspension of the dry salt (II) in tetrahydrofuran (250 ml.) was added dropwise a solution of benzenesulfonyl chloride (25 ml.) in tetrahydrofuran (25 ml.), the temperature of the reaction being kept between 0-5°. After 1 hour, sodium acetate trihydrate (18.8 g.) was added to the reaction mixture, stirring continued at room temperature for 0.5 hour, then at 50-60° for 0.5 hour. The mixture was filtered and the filtrate concentrated, *in vacuo*, to a small bulk. On cooling, the product crystallized out and it was recrystallized from a mixture of tetrahydrofuran and *n*-hexane. It weighed 9.2 g. (47% based on the ester), m.p. 249-251°,  $\lambda$  max (95% ethanol), 267 (log  $\epsilon$  3.38), 275 (log  $\epsilon$  3.30), 318  $\mu$  (log  $\epsilon$  3.88).

Its n.m.r. spectrum ((CH<sub>3</sub>)<sub>2</sub>SO) showed the pyrazine protons as an AB system  $\delta$  8.79 and 8.67 ( $J = 2.2$  c.p.s.) (6), the phenyl protons as a multiplet between  $\delta$  8.25 and 7.60 and the exchangeable protons as a relatively sharp but broad signal at  $\delta$  12.76.

*Anal.* Calcd. for C<sub>12</sub>H<sub>8</sub>N<sub>4</sub>O<sub>3</sub>S: C, 45.00; H, 2.51; N, 17.49. Found: C, 44.90; H, 2.47; N, 17.21.

## 3-Hydroxylumazine (IV).

A solution of III (0.32 g., 0.001 mole) in 10% sodium hydroxide solution (5 ml.) was boiled under reflux for 2-5 minutes, cooled and acidified with dilute (1:3) hydrochloric acid. The yellow solid (0.08 g., 44%) was recrystallized from 10% aqueous acetone, m.p. 325-328°,  $\lambda$  max (95% ethanol) 234 (log  $\epsilon$  4.09), 322  $\mu$  (log  $\epsilon$  3.78).

In its n.m.r. spectrum ((CH<sub>3</sub>)<sub>2</sub>SO) signals due to the pyrazine protons were observed again as an AB system  $\delta$  8.76, 8.65 ( $J = 2.2$  c.p.s.) and the exchangeable protons as an almost flat signal between  $\delta$  12.50 and 10.40.

*Anal.* Calcd. for C<sub>8</sub>H<sub>4</sub>N<sub>4</sub>O<sub>3</sub>: C, 40.01; H, 2.23; N, 31.11. Found: C, 39.90; H, 2.53; N, 31.22.

Prolonged hydrolysis invariably decreased the yield of this product.

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## REFERENCES

- (1) R. M. Cresswell, H. K. Maurer, T. Strauss, and G. B. Brown, *J. Org. Chem.*, **30**, 408 (1965).
- (2) W. Pfeleiderer and W. Hutzenlaub, *Angew. Chem.*, **77**, 1136 (1965).
- (3) For a summary of references for this method, see L. Bauer, C. N. V. Nambury and D. Dhawan, *J. Heterocyclic Chem.*, **1**, 275 (1964).
- (4) This effect was noted in several simpler potentially tautomeric heteroaromatic systems such as in 3-isoxazolones and 2-pyridones. In chloroform, 2-benzenesulfonyloxy-4,5-dimethyl-3-isoxazolone showed a carbonyl band at 1724 cm<sup>-1</sup> while 4,5-dimethyl-3-isoxazolone has the highest frequency band (between 1500 and 1800 cm<sup>-1</sup>) at 1666 cm<sup>-1</sup>, [C. L. Bell, C. N. V. Nambury and L. Bauer, *Tetrahedron*, **20**, 165 (1964)]. Similarly, in Nujol, 1-arenesulfonyloxy-2-pyridones exhibit the ring carbonyl bands around 1690 cm<sup>-1</sup>, [L. A. Paquette, *J. Am. Chem. Soc.*, **87**, 5186 (1965); M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **84**, 23 (1964)], while 2-pyridone has a band at 1650 cm<sup>-1</sup>. In the same vein, 3-benzenesulfonyloxy-5,6-dihydrouracil [C. D. Hurd and L. Bauer, *J. Am. Chem. Soc.*, **76**, 2791 (1954)] and 3-hydroxy-5,6-dihydrouracil [C. D. Hurd, C. M. Buess, and L. Bauer, *J. Org. Chem.*, **19**, 1140 (1954)] showed carbonyl absorptions at 1730, 1710 and 1710, 1675 cm<sup>-1</sup> respectively (in KBr). 3-Benzenesulfonyloxy- and 3-hydroxy-2,4-quinazolinediones [C. M. Buess, and L. Bauer, *ibid.*, **20**, 33 (1955)] exhibited carbonyl bands at 1750, 1710 and 1735, 1710 cm<sup>-1</sup> respectively (in Nujol). Similarly, in Nujol, *N*-benzenesulfonyloxyphthalimide showed the carbonyl bands at 1795 and 1745 cm<sup>-1</sup> [L. Bauer and S. V. Miarka, *J. Am. Chem. Soc.*, **79**, 1983 (1957)] and *N*-hydroxyphthalimide at 1715 and 1666 cm<sup>-1</sup> [D. E. Ames and T. F. Grey, *J. Chem. Soc.*, 3518 (1955)].
- (5) Prepared by the method of R. C. Ellingson and R. L. Henry [*J. Am. Chem. Soc.*, **71**, 2798 (1949)]. Its n.m.r. spectrum showed a singlet at  $\delta$  4.02 (OCH<sub>3</sub>) and at  $\delta$  9.02 (the pyrazine protons). The infrared spectrum showed a strong band at 1725 cm<sup>-1</sup> (C=O of ester).
- (6) S. Matsuura and T. Goto [*J. Chem. Soc.*, 1773 (1963)] have reported the n.m.r. spectrum of pteridine (CDCl<sub>3</sub>) and have found H-6 and H-7 at  $\delta$  9.15 and 9.33, respectively,  $J = 1.7$  c.p.s.

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