52%. Recrystallization from 95% ethanol gave white prisms, m.p. 230–231° (lit.[3] 231–232°). The infrared spectrum showed absorption at 2.79μ, 2.99μ, 5.78μ, 6.42μ and was identical with that of an authentic sample of 1,12-dimethyl-7-isopropyl-9-oxo-10-oxa-11-hydroxy-8-nitro-1,2,3,4,9,10,-11,12-octahydrophenanthrene (III).[6] The ultraviolet spectrum showed: $\lambda_{max}^{95\%\ EtOH}$ 293 mμ(log ε 3.19).[6]

Acknowledgment. We gratefully acknowledge the support of this work by the Research Corporation of New York.

CONTRIBUTION NO. 1496 FROM
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(6) M. Tsutsui, Ph.D. Thesis, Yale University, 1955.

Photochemical Oxidation of 5-Nitro-2-furfuryl Iodide

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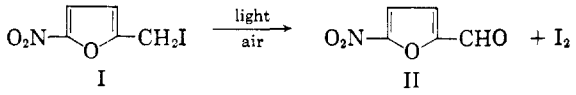
Received August 25, 1958

The oxidation of certain substituted bromomethanes to aldehydes by means of dimethyl sulfoxide was recently described by Kornblum and associates.[1] We wish to report a formally similar reaction, the photochemical air oxidation of 5-nitro-2-furfuryl iodide, I, to 5-nitro-2-furfural, II, and iodine.



I II

The synthesis of I was desirable in connection with this laboratory's continuing interest in chemotherapeutic nitrofurans.[2] It was readily effected by the reaction of 5-nitro-2-furfuryl nitrate with sodium iodide in acetone.

Chloroform solutions of I were stable for at least 2 weeks in the dark but liberated iodine when exposed to light. This was accompanied by the appearance of a new peak at 5.89μ in the infrared spectrum, corresponding to the carbonyl absorption of II. Treatment of the crude iodine-free product with semicarbazide hydrochloride gave the semicarbazone of II, although in unsatisfactory yield. As an estimate of the time necessary for completion of the reaction and a more quantitative estimate of the yield was desired, the reaction rate was followed by sodium thiosulfate titration and by infrared analysis of the reaction mixture. The results showed the reaction to be essentially complete in 70 hr., and the maximum yield of II to be 54%. By chromatography on alumina a 34% yield of II was isolated and identified by its infrared spectrum and conversion to 5-nitro-2-furfural phenylhydrazone in 90% yield.

(1) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, 79, 6562 (1957).

(2) For a recent paper in this series, see J. G. Michels and G. Gever, *J. Am. Chem. Soc.*, 78, 5349 (1956).

EXPERIMENTAL[3,4]

5-Nitro-2-furfuryl nitrate. To 720 ml. of acetic anhydride was added, with stirring, 189 g. (2.1 moles) of concentrated nitric acid followed by 108 g. (1.1 mole) of furfuryl alcohol. The temperature was held at 20–25° by means of an ice bath. The total time of addition was 12–15 min. The mixture was heated to 40° for 1 hr. and then cooled to 25°. One l. of water and 300 g. of trisodium phosphate were added and the temperature was raised to 60° for 1 hr., cooled to 10–15° and the solid which separated was collected. The yield was 88 g. (42%) m.p. 34–36°. Recrystallization from isopropyl alcohol raised the m.p. to 36–36.5°.

Anal. Calcd. for $C_5H_4N_2O_6$: C, 31.92; H, 2.14; N, 14.89. Found: C, 32.05; H, 2.34; N, 14.75.

5-Nitro-2-furfuryl iodide. A solution of 179 g. (0.95 mole) of 5-nitro-2-furfuryl nitrate in 250 ml. of acetone was added to a saturated solution of 150 g. (1.00 mole) of sodium iodide in acetone. After standing in the cold for 6 hr. the sodium nitrate was removed by filtration and the acetone was evaporated from the filtrate at 30° by means of a rotary evaporator. The residue was diluted with 100 ml. of isopropyl alcohol and chilled. The orange crystals were collected, washed with a little isopropyl alcohol and dried. The yield was 184 g. (76%) m.p. 58–59°.

Anal. Calcd. for $C_5H_4INO_3$: C, 23.74; H, 1.59; N, 5.54; I, 50.17. Found: C, 23.91; H, 1.53; N, 5.64; I, 50.4.

Rate determinations. Two 1-l. 1% chloroform solutions of 5-nitro-2-furfuryl iodide were allowed to stand 70 hr. in 2-l. Erlenmeyer flasks continually exposed to laboratory light. Periodically 10-ml. aliquots were removed and titrated with 0.1*N* sodium thiosulfate to the disappearance of the pink color. Infrared spectra,[5] were determined in 0.5-mm. matched sodium chloride cells with chloroform in the solvent cell. A standard curve of analytically pure 5-nitro-2-furfural was prepared and was shown to obey Beer's Law over the concentration range studied.

Isolation and characterization of 5-nitro-2-furfural. After 90–100% of the iodine had been liberated, the two solutions were combined and shaken with 200 ml. of 10% sodium thiosulfate solution to remove the iodine. The chloroform layer was separated, dried, and the chloroform removed at 30–40° by a rotary vacuum evaporator. The residue was 10 g. of dark, golden liquid. Several small-scale experiments indicated that purification could be effected by chromatography and the remaining product, 7.21 g., in about 50 ml. of benzene was added to a column containing 500 g. of acid-washed alumina. Development and elution with benzene yielded 1.54 g. of slightly impure 5-nitro-2-furfuryl iodide, m.p. 49–52, in the 350 ml. of eluent. The next 2 l. of benzene yielded 2.46 g. of 5-nitro-2-furfural. The infrared spectrum of this sample was identical with the spectrum of authentic 5-nitro-2-furfural. The corrected yield, based on unrecovered 5-nitro-2-furfuryl iodide, was 34%. To provide a solid derivative, the product was dissolved in ethanol and treated with an aqueous solution containing 2.5 g. of phenylhydrazine hydrochloride. The red precipitate was collected, washed with ethanol and water, and dried at 60°. The yield was 3.5 g. (90%) m.p. 190–192°. λ_{max}^{EtOH} 465 mμ (log ε 4.32).

(3) All melting points were taken on a calibrated Fisher-Johns apparatus.

(4) Microanalyses were carried out by Mr. Gordon Ginther and the ultraviolet spectra were determined by Mr. Curtis Eaton and Mrs. Catherine Gravesen.

(5) A Perkin-Elmer Model 21 instrument employing sodium chloride optics was used.

Authentic 5-nitro-2-furfural phenylhydrazone melts at 190–192°. $\lambda_{max}^{60\%\ EtOH}$ 467 mμ (log ε 4.31).[6,7]

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(6) Unpublished results obtained in these laboratories.
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A Convenient Synthesis of 4(5)-Amino-5(4)-imidazolecarboxamide Hydrochloride[1]

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Received August 27, 1958

4(5)-Amino-5(4)-imidazolecarboxamide was first isolated by Stetten and Fox[2] from a culture of *E. coli* inhibited by sulfanilamide. It has since been shown to be the precursor of purines in the *de novo* synthesis of nucleic acids (in these biosynthetic processes it occurs as the ribotide).[3] It has also been shown that exogenous 4(5)-amino-5(4)-imidazolecarboxamide greatly increases the incorporation of guanine into the nucleic acids of certain tumors in mice and significantly increases its incorporation in normal body tissues.[4] It appears to be an *in vitro* inhibitor of guanase.[5,6]

None of the several synthetic methods which have been developed by various investigators[7] is convenient for the preparation of large quantities of this biologically important compound. An examination of these routes to 4(5)-amino-5(4)-imidazolecarboxamide led to the conclusion that the procedure of Shaw and Woolley[7a] could be most readily adapted to a large scale preparation of the compound. The conversion of ethyl cyanoacetate in three steps to phenylazomalonamamidine hydrochloride is quite good and can be carried out on large amounts of material. The reductive formylation of phenylazomalonamamidine hydrochloride can also be performed on a large scale, but the isolation of the resulting formylaminomalonamamidine and dry fusion of this material to give 4(5)-amino-5(4)-imidazolecarboxamide is not adaptable to large quantities. In addition, the fusion yields a green specimen of the imidazole which is difficult to free from its pigmented impurities.

We have found that phenylazomalonamamidine hydrochloride can be reduced in formic acid solution either catalytically or with zinc dust and, after removal of the palladium-on-charcoal catalyst or the excess zinc dust, cyclized to 4(5)-formylamino-5(4)-imidazolecarboxamide by simply refluxing the now colorless solution.[8] The removal of the excess formic acid gave a white solid which was triturated with ethanol to remove the by-product formanilide and, if the zinc reduction was used, the 4-formylamino-5-imidazolecarboxamide was then recrystallized from water to rid it of zinc salts. When the catalytic reduction was employed simple trituration gave material which was about 98% pure.

The 4(5)-formylamino-5(4)-imidazolecarboxamide was easily converted to 4(5)-amino-5(4)-imidazolecarboxamide hydrochloride by refluxing it in dilute hydrochloride acid. The white material obtained was usually sufficiently pure to use without further purification. Up to 100 g. of both compounds has been prepared in one reaction sequence using the zinc reduction, but better yields were obtained from the runs using catalytic reduction, the average yield of 4(5)-amino-5(4)-imidazolecarboxamide hydrochloride being 70%.

Pure 4(5)-amino-5(4)-imidazolecarboxamide was readily prepared from a water solution of its hydrochloride by treatment with Dowex-1.

EXPERIMENTAL

4(5)-Formylamino-5(4)-imidazolecarboxamide and 4(5)-amino-5(4)-imidazolecarboxamide hydrochloride. Method A (zinc reduction). Phenylazomalonamamidine hydrochloride (25.0 g.) was added in portions to a stirred suspension of zinc dust (50 g.) in 98% formic acid (225 ml.) at 25°. The excess zinc dust was removed by filtration; the filtrate was refluxed for 8 hr. and then taken to dryness *in vacuo*. The solid residue was dissolved in hot water (700 ml.) and the resulting solution allowed to stand overnight in a refrigerator. The 4(5)-formylamino-5(4)-imidazolecarboxamide which crystallized from the solution was removed by filtration and dried *in vacuo* over phosphorus pentoxide: yield, 4.45 g. (28%); $\lambda_{max}^{pH\ 7}$ 269 mμ (ε 12,900) [lit.,[9] $\lambda_{max}^{pH\ 6}$ 268 mμ (ε 10,900)].

Anal. Calcd. for $C_5H_6O_2N_6$: C, 38.97; H, 3.94; N, 36.37. Found: C, 39.26; H, 4.20; N, 36.29.

The filtrate from the isolation of the 4(5)-formylamino-5(4)-imidazolecarboxamide was saturated with hydrogen sulfide. The precipitated zinc sulfide was removed by filtration and the excess hydrogen sulfide by concentration of the solution *in vacuo*. The solution was then acidified with dilute hydrochloric acid, refluxed for 15 min., and evapo-

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(8) The ultraviolet spectrum of the solution before reflux showed that it contained an appreciable quantity of 4(5)-formylamino-5(4)-imidazolecarboxamide indicating that some cyclization had occurred during the reduction procedure.
(9) E. Shaw, *J. Biol. Chem.*, **185**, 439 (1950).