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REACTIVITY OF HETEROCYCLIC COMPOUNDS IN NITRATION.
8.* NITRATION OF 3-HYDROXYPYRIDINE AND ITS SUBSTITUTED FORMS

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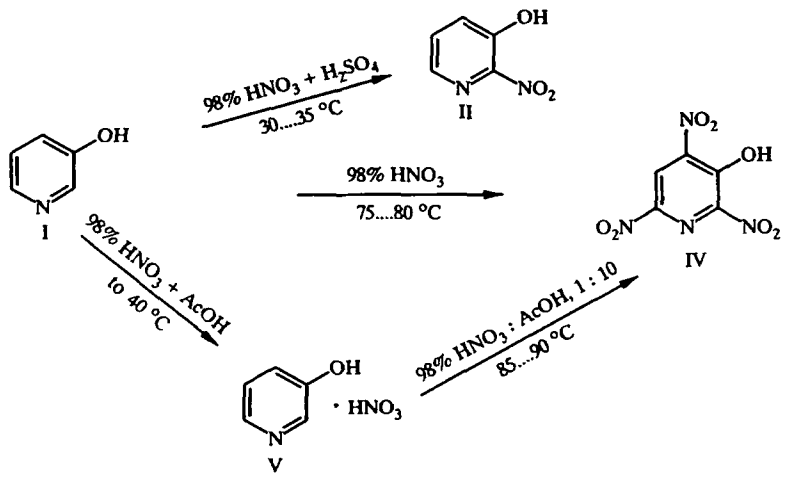
Nitration of 3-hydroxypyridine and its substituted forms has been studied under various conditions. It is shown that, depending on the reaction temperature and the nitrating agent, the end products of the synthesis can be 3-hydroxy-2,6-dinitropyridine or 3-hydroxy-2,4,6-trinitropyridine. The possibility of substitutional nitration of iodine derivatives of 2- and 3-hydroxypyridine is demonstrated.

Nitration of 3-hydroxy derivates of pyridine involves aspects of both theoretical and practical importance, since nitro derivatives of 3-hydroxypyridine (I) are characterized by a high biological activity [2, 3].

Nitration of compound I by a mixture of sulfuric and nitric acids formed 3-hydroxy-2-dinitropyridine (II) [4], which was converted with a 36% yield to 3-hydroxy-2,6-dinitropyridine (III) in the presence of acetic anhydride (3-hydroxy-2,4,6-trinitropyridine (IV) was also isolated as an impurity with a yield no greater than 1% [5]). However, except for the melting point (120°C), no other properties of this compound are given in that work.



We studied the nitration of 3-hydroxypyridine I with various nitrating agents. This confirmed the data of [4] to the effect that treatment of this compound with a mixture of sulfuric and nitric acids at 30-35°C formed only the mononitro derivative II. Raising the reaction temperature from 40 to 80°C and using excess concentrated nitric acid cause a decrease in yield of compound II. Nitration of hydroxypyridine I with concentrated nitric acid at 75-80°C formed a product with a melting point of 119-120°C and a 25% yield. On the basis of data of elemental analysis and NMR and IR spectra, it was identified as 3-hydroxy-2,4,6-trinitropyridine IV.

*For Communication 7, see [1].

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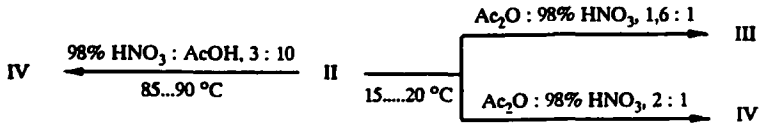
A study of the structure of compound IV showed that it is present in its hydroxy form. Its IR spectrum contains the absorption band of the OH group at 3260 cm^{-1}. The PMR spectrum includes a signal with a chemical shift of 7.85 ppm, which can be assigned to the proton of the hydroxyl group.

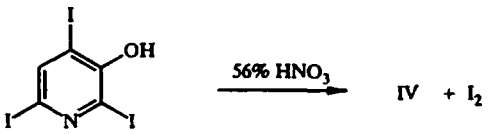
In strong mineral acids, 3-hydroxypyridine I and its derivatives undergo protonation [4], and therefore, further study of the nitration involved the use of a mixture of concentrated nitric acid and acetic acid or acetic anhydride.

Treatment of hydroxypyridine I with mixtures of acetic and concentrated nitric acids of different compositions showed that up to 40°C, only the nitrate of this compound (V) is formed. Raising the reaction temperature to 85-90°C and a 10-15-fold excess of nitric acid result in nitration of compound V to the trinitro derivative IV, the yield of which does not exceed 40%. An increase in yield of compound IV to 62-65% can be achieved by nitrating 3-hydroxy-2-nitropyridine II with a mixture of acetic and 98% nitric acids (10:3 m.pts.) at 85-90°C for 3 h.

A study of the nitration of compound II with a mixture of acetic anhydride and concentrated nitric (98%) acid at 15-20° showed that the outcome of the reaction depends on the ratio of the components of this mixture. Thus, for a ratio $Ac_2O:HNO_3$ (1.5-1.6):1, the dinitro substituted form III is formed in 37% yield, and of acetic anhydride, in a twofold excess, the trinitro derivative IV (yield, 40-41%) is formed. A further increase of the amount of acetic anhydride and of the reaction temperature does not result in an increase in yield of compound IV.

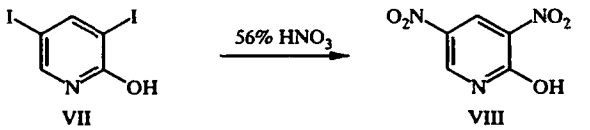


It is well known that hydroxypyridine I readily undergoes iodination to 3-hydroxy-2,4,6-triiodopyridine (VI) [6]. We studied the substitutional nitration of the latter. We found that when compound VI is boiled in dilute (56%) nitric acid for 5-6 h, all three iodine atoms are replaced, and trinitropyridine IV is formed in 70% yield.



VI

The reaction of substitutional nitration is apparently of a general character. Thus, treatment of 2-hydroxy-3,5-diiodopyridine (VII) with weak nitric acid forms 2-hydroxy-3,5-dinitropyridine (VIII) in 72-75% yield:



VII VIII

EXPERIMENTAL

The IR spectrum was recorded on a Specord IJ-75 instrument in a KBr pellet. The PMR spectrum was obtained on a Bruker WH-90/DS spectrometer (60 MHz); the solvent was acetone-D_6, and the internal standard was TMS. The ^{13}C NMR spectrum was taken on a Bruker WP-200 instrument in DMSO-D_6.

2-Hydroxy-3,5-diiodo- and 3-hydroxy-2,4,6-triiodopyridine were prepared using the methods of [8] and [6], respectively.

3-Hydroxy-2,6-dinitropyridine (III). To a mixture of 2.8 ml of acetic anhydride and 1.24 ml (0.028 mole) of 98% nitric acid at 0°C was added in portions 1 g (0.007 mole) of compound II. The reaction mixture was kept for 1 h at 20°C, poured into 25 ml of cold water, and evaporated in a vacuum (15-20 Torr; bath temperature, 60-70°C). The residue in the flask was treated with hot benzene. When the benzene solution cools, crystals of compound III precipitate out, and are filtered and dried. Yield, 0.49 g (37%); mp 132-133°C. Lit. mp 132°C [4].

3-Hydroxyyridine Nitrate (V). A. To a solution of 1 g (0.01 mole) of compound I in 25 ml of diethyl ether at 15-20°C is added dropwise 5 ml of 65% nitric acid. The formed white precipitate of 3-hydroxypyridine nitrate is filtered off, washed with 5-10 ml of ether, and dried. There is obtained 1.45 g of product V. Yield, 92%; mp 127-128°C (from water). Found, %: C 37.64; H 3.58; N 17.80. $C_5H_6N_2O_4$. Calculated, %: C 37.97; H 3.79; N 17.72.

B. Compound I treated with mixtures of different compositions (10:2, 10:3, 10:5 m.pts.) of AcOH and HNO_3 at a temperature not above 40°C formed nitrate V, identical to the sample obtained by method A (absence of mp depression of the mixed sample). Yield, 88-90%; mp 127-128°C (from water).

3-Hydroxy-2,4,6-trinitropyridine (IV). A. To 7 ml (0.16 mole) of 98% nitric acid at 20-25°C is added for 1 h in small portions 1 g (0.1 mole) of compound I. The reaction mixture is gradually heated to 75-80°C and kept at this temperature for 5-6 h. The solution obtained is cooled to room temperature, poured into 20 ml of water, and evaporated at reduced pressure. The residue is treated with hot benzene (see separation of compound III). There is obtained 0.5-0.57 g (22-25%) of compound IV; mp 119-120°C (from benzene). Lit. mp 120°C [4]. IR spectrum: 1595 (C=C), 1625 (C=N), 1320, 1350, 1540, 1560 (C−NO_2), 3260 cm^{-1} (C−OH). UV spectrum (in water), λ_{max} (log ε): 342 nm (3.83). PMR spectrum: 8.98 (1H, s, C−H), 7.85 ppm (1H, s, C−OH). ^{13}C NMR spectrum: 123 ($C_{(5)}$), 149 ($C_{(2)}$, $C_{(4)}$, $C_{(6)}$), 154.5 ppm ($C_{(3)}$). Found, %: C 24.10; H 0.85; N 25.84. $C_5H_2H_4O_7$. Calculated, %: C 24.30; H 0.87; N 26.00.

B. To a mixture of 40 ml of acetic anhydride and 18 ml (0.42 mole) of 98% nitric acid at a temperature not above 15°C is added 10 g (0.07 mole) of compound II. The reaction mixture is kept for 1 h at 29-31°C, cooled to 20°C, and poured into 200 ml of water. After the usual treatment (see separation of compound III), 6.7 g (41%) of product IV is obtained; mp 119-120°C (from benzene).

C. To a mixture of 10 ml of acetic acid and 5 ml of 98% nitric acid at 25-35°C is added 1 g (0.01 mole) of compound I, and the mixture is heated to 80-85°C and kept at this temperature for 4-5 h. The mass is cooled to 20°C, and diluted with 25-30 ml of water. Separation is carried out as in A. Yield of product IV, 0.94 g (40%); mp 119-120°C (from benzene).

D. To a mixture of 10 ml of acetic acid and 2 ml of 98% nitric acid at 30-40°C is added 1 g (0.006 mole) of compound V. The reaction mass is kept for 3 h at 85-90°C, and cooled to 20°C. Separation is carried out as in A. Yield of product IV, 0.59 g (40%); mp 119-120°C (from benzene).

E. To a mixture of 10 ml of acetic acid and 2 ml of 98% nitric acid at 25-30°C is added 1 g (0.007 mole) of compound II. The reaction mass is kept for 3 h at 85-90°C, cooled to 20°C, and diluted with 20 ml of water. Separation is carried out as in A. Yield of product IV, 1.05 g (65%); mp 119-120°C (from benzene). Samples of product IV obtained by use of methods A−E do not depress the mp of the mixed sample.

Substitutional Nitration of Iodine Derivatives of 2-Hydroxy- and 3-Hydroxypyridine (General Method). The derivative in an amount of 0.01 mole is boiled for 5-6 h in 40-50 ml of 56% nitric acid until iodine is completely separated and the reaction mixture turns colorless, and is then evaporated. 2-Hydroxy-3,5-dinitropyridine (VIII) is obtained from 2-hydroxy-3,5-diiodopyridine. Yield, 72-75%; mp 175-176°C (from water). Lit. mp 175°C [7]. Product IV is obtained from 3-hydroxy-2,4,6-triiodopyridine. Yield, 70%; mp 119-120°C (from benzene).

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