[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

An Unusual Formation of a Disulfide from a Sulfide

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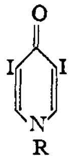
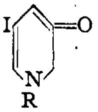
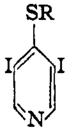
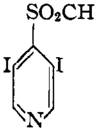
The known clinical efficacy of 3,5-diiodo-4-pyridone-N-acetic acid (I) and other pyridones as urographic X-ray contrast media[2] suggested that mercaptopyridine derivatives should be of interest for similar purposes.

In the diiodopyridone series, N-alkylation is favored over O-alkylation. For example, 3,5-diiodo-4-pyridone (II) and the corresponding 2-pyridone (V) readily react in alkaline medium with dimethyl sulfate to yield the N-methyl derivatives III and VI[3], respectively. With chloroacetic acid II and V yield the N-acetic acid compounds I[3,4] and IV.[5,6] To obtain the O-alkyl compounds, the silver salts of the diiodopyridones are used. In contrast, in the mercapto pyridine series S-alkylation is favored over reaction at the nitrogen atom.[7] Consequently it was expected that the reaction between 3,5-diiodo-4-mercaptopyridine (VII) and chloroacetic acid in alkaline solution would yield the S-acetic acid (VIII).


I R = CH_2COOH
II R = H
III R = CH_3


IV R = CH_2COOH
V R = H
VI R = CH_3

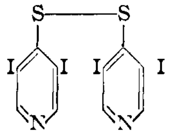

VII R = H
VIII R = CH_2COOH
IX R = CH_3
X R = CH_2CH_2COOH

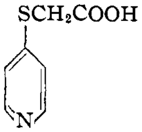

XI

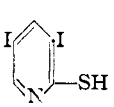
Confirmation of structure VIII as opposed to the N-acetic acid structure was obtained in an unexpected way. It was observed that an aqueous solution of the sodium salt of VIII became turbid after standing for a few minutes and slowly deposited a neutral substance. The same substance was formed when the free acid was heated in Cellosolve.

It was first thought that this neutral substance was the methyl sulfide IX formed by decarboxylation. However, methylation of 3,5-diiodo-4-mercaptopyridine with methyl sulfate gave a product which melted 110° lower than the substance in question and which was shown to have structure IX by oxidation to the sulfone XI.

Elementary analysis indicated that the neutral decomposition product was the disulfide XII, formed with loss of the acetic acid side chain.


XII


XIII


XIV

This structure was confirmed by iodine oxidation of VII to XII.

The S-propionic acid (X), prepared from VII by treatment with β-bromopropionic acid, decomposed in sodium bicarbonate solution under the same conditions as VIII to give the same product XII.

The uniodinated 4-mercaptopyridine S-acetic acid (XIII) is reported a stable compound[7] and we found that it may be recovered quantitatively from a solution of its sodium salt that has been boiled for twenty-four hours.

It was thought that the facile decomposition of VIII might be due to the steric effect of the large iodine atoms and that light might be shed on the reaction by a study of the derivatives of 3,5-diiodo-2-mercaptopyridine (XIV). Unfortunately this substance reacted with alkaline chloroacetate solution only to lose sulfur with the formation of 3,5-diiodo-2-pyridone (V) which then yielded the corresponding N-acetic acid (IV). Since silver salts of pyridones have been used to effect O-alkylation, the silver salt of XIV was investigated. It gave no acidic product with chloroacetic acid, but with ethyl bromoacetate it gave a good yield of the ethyl ester of 3,5-diiodo-2-pyridone-N-acetic acid, sulfur again having been lost.

Alkaline permanganate oxidation of VIII gave 3,5-diiodo-4-pyridone (II) instead of a sulfone; this reaction also serves as evidence that the side chain is linked to the sulfur atom.

Experimental

(1) **3,5-Diiodo-4-mercaptopyridine-S-acetic Acid (VIII).**—Thirty-two and six-tenths grams (0.09 mole) of 3,5-diiodo-4-mercaptopyridine[8] (VII) was dissolved in a hot solution of 10 g. (0.25 mole) of sodium hydroxide in 500–600 ml. of hot water, treated with 10 g. (0.11 mole) of chloroacetic acid dissolved in sodium carbonate solution

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[1] Present address: American Cyanamid Co., Calco Chemical Division, Bound Brook, N. J.

[2] Maier-Bode and Altpeter, "Das Pyridin und seine Derivate," Wilhelm Knapp Verlag, Halle, 1934, p. 138–141 (photo-lithoprint reproduction by Edwards Brothers, Ann Arbor, Mich., 1943).

[3] Dohrn and Diedrich, *Ann.*, **494**, 284 (1932).

[4] Baker and Briggs, *J. Soc. Chem. Ind.*, **62**, 189 (1948).

[5] Rath, *Ann.*, **486**, 71 (1931).

[6] Sugii and Shindo, *J. Pharm. Soc. Japan*, **51**, 416 (1931): *C. A.*, **25**, 4549^3 (1931).

[7] King and Ware, *J. Chem. Soc.*, 873 (1939).

[8] See ref. 2. An improved procedure for preparing halogenated pyridones will be published shortly.

and heated on the steam-bath for two hours. At this point, if necessary, the solution was clarified by filtration, acidified with acetic acid and filtered. The filtrate was then treated dropwise with hydrochloric acid until each drop no longer produced a precipitate. The combined crops gave a theoretical yield of product, m. p. 175–177°. No solvent was found suitable for crystallization of large quantities of material without decomposition. The analytical sample crystallized from ethanol as fine white needles, m. p. 180–181°.

Anal. Calcd. for $C_7H_5I_2NO_2S$: C, 19.97; H, 1.20. Found: C, 20.22; H, 1.42.

The substance dissolved readily in hot Cellosolve and gave fine crystals on cooling which, however, melted substantially higher than the pure acid because of the presence of a high melting neutral impurity. Leaching with hot sodium carbonate left an insoluble residue of 3,5-diiodo-4-pyridyl disulfide (XII), which after repeated recrystallization from dilute pyridine melted at 230–231°.

Anal. Calcd. for $C_{10}H_4I_4N_2S_2$: C, 16.59; H, 0.56; N, 3.87; S, 8.84. Found: C, 16.61; H, 0.92; N, 4.21; S, 9.03.

A solution of the pure acid VIII in sodium bicarbonate became turbid in ten minutes. After it was found repeatedly that filtration gave only temporary clarification, the solution was allowed to stand for one week and the collected solid examined. By melting point and mixed melting point it proved identical with XII.

(2) **Preparation of 3,5-Diiodo-4-pyridyl Disulfide (XII) from 3,5-Diiodo-4-mercaptopyridine (VII).**—A solution of 3.6 g. (0.01 mole) of 3,5-diiodo-4-mercaptopyridine (VII) in 50 ml. of water containing 2 g. of sodium hydroxide was treated in the cold with a potassium iodide solution of 1.3 g. (0.005 mole) of iodine. A precipitate formed immediately. After crystallization from dilute pyridine, it melted at 228–229° and showed no depression in melting point on admixture with the product obtained by the decomposition of the acid VIII.

(3) **3,5-Diiodo-4-mercaptopyridine-S-β-propionic Acid (X).**—A solution of 30 g. (0.083 mole) of 3,5-diiodo-4-mercaptopyridine in 500 ml. of water containing 10 g. of sodium hydroxide was heated on the steam-bath for two hours with 18 g. (0.12 mole) of β-bromopropionic acid dissolved in a small volume of sodium carbonate solution. Acidification with hydrochloric acid to congo paper gave 30.5 g. (85%) of product, m. p. 194–199°. Crystallization from ethyl methyl ketone gave white needles, m. p. 212–213°.

Anal. Calcd. for $C_8H_7I_2N_2O_2S$: C, 22.08; H, 1.62. Found: C, 22.61; H, 1.64.

A sodium bicarbonate solution of this acid slowly deposited a solid which proved identical by melting point and mixed melting point with the disulfide XII.

(4) **3,5-Diiodo-S-methyl-4-mercaptopyridine (IX).**—A potassium hydroxide solution of 36.3 g. (0.1 mole) of 3,5-diiodo-4-mercaptopyridine was methylated on the steam-bath in the usual way with 13 g. (0.103 mole) of dimethyl sulfate. There was obtained 17 g. (45%) of product, m. p. 120–121°. Recrystallization from dilute pyridine raised the m. p. to 122.5–123°.

Anal. Calcd. for $C_6H_5I_2NS$: N, 3.72. Found: N, 3.75.

(5) **3,5-Diiodo-4-methylsulfonylpyridine (XI).**—One and nine-tenths grams (0.005 mole) of 3,5-diiodo-S-methyl-4-mercaptopyridine (IX) was dissolved in 100–150 cc. of glacial acetic acid and treated at room temperature with a solution of 1.2 g. (0.0076 mole) of potassium permanganate in approximately 100 cc. of water. Reaction was instantaneous. Destruction of the manganese dioxide with sodium bisulfite and chilling gave 1.2 g. (57%) of white needles, m. p. 149–152°. Recrystallization from dilute pyridine raised the m. p. to 165–166°.

Anal. Calcd. for $C_6H_5I_2NO_2S$: C, 17.62; H, 1.23. Found: C, 17.72; H, 1.40.

(6) **Reaction of 3,5-Diiodo-2-mercaptopyridine (XIV) with Alkaline Chloroacetate Solution.**—A solution of 10 g. (0.027 mole) of 3,5-diiodo-2-mercaptopyridine[3] and 5 g. of sodium hydroxide in 500 cc. of water was treated with a sodium carbonate solution of 4.2 g. (0.044 mole) of chloroacetic acid and heated on the steam-bath for two hours. Acidification with acetic acid precipitated a product, m. p. 256.3–261.3°. Recrystallization from 900 cc. of ethanol gave 6.5 g. of product, m. p. 269.4–270.4°. Sodium decomposition showed sulfur to be absent. Admixture with 3,5-diiodo-2-pyridone (V) had no effect on the melting point. Methylation in alkaline solution with dimethyl sulfate gave a product, m. p. 229–231°. The melting point reported[4] for N-methyl-3,5-diiodo-2-pyridone (VI) is 227°.

In a similar experiment with the same quantities of starting material the mixture was heated for approximately six hours. Working up as before and recrystallization from alcohol gave 7.8 g. of product, m. p. 235–236°, which showed no depression in m. p. on admixture with authentic 3,5-diiodo-2-pyridone-N-acetic acid[5] (IV). Sodium decomposition showed sulfur to be absent.

Anal. Calcd. for $C_7H_5I_2NO_3$: C, 20.76; H, 1.24. Found: C, 20.60; H, 1.49.

(7) **Reaction of Silver Salt of 3,5-Diiodo-2-mercaptopyridine with Ethyl Chloroacetate.**—Five grams (0.014 mole) of 3,5-diiodo-2-mercaptopyridine (XIV) was dissolved in alkali and treated with an ammoniacal solution of 2.7 g. (0.016 mole) of silver nitrate. The precipitated, air-dried silver salt weighing 6.2 g., was refluxed with 25 g. (0.15 mole) of ethyl bromoacetate in 300 cc. of ethanol for twenty-four hours. After evaporation of the alcohol, the residue was leached with potassium cyanide solution and filtered, leaving 4 g. (67%) of ethyl 3,5-diiodo-2-pyridone-N-acetate, m. p. 144–145°. Recrystallization from dilute pyridine or ethanol raised the m. p. to 149–150°. Sodium decomposition showed the absence of sulfur and the presence of iodine and nitrogen. Admixture with an authentic specimen of the ester had no effect on the m. p.

(8) **Ethyl 3,5-Diiodo-2-pyridone-N-acetate.**—Five grams of 3,5-diiodo-2-pyridone-N-acetic acid (IV) was refluxed for one-half hour in 300 ml. of absolute ethanol containing 3 cc. of concentrated sulfuric acid. The solution was evaporated to about one-fourth its volume and diluted with sodium bicarbonate solution. Thus was precipitated 5.3 g. of ester, m. p. 148–150°. The analytical sample melted at 150–150.5°.

Anal. Calcd. for $C_9H_9NO_3I_2$: C, 24.96; H, 2.10. Found: C, 24.86; H, 2.08.

(9) **Permanganate Oxidation of 3,5-Diiodo-4-mercaptopyridine-S-acetic Acid (VIII).**—Five grams (0.012 mole) of the acid was dissolved in a minimum of potassium hydroxide and treated dropwise at room temperature with an aqueous solution of 2.5 g. (0.016 mole) of potassium permanganate. In order to destroy the manganate which quickly began to accumulate, the solution was then buffered with Dry Ice. Decolorization was very slow and the permanganate addition took four hours. After filtration of the manganese dioxide, the solution was decolorized with bisulfite and acidified with acetic acid. The starting material was precipitated unchanged and identified by m. p., mixed m. p. and its neutral equivalent of 420 (theoretical 421).

Evaporation of the filtrate gave a solid melting above 270°. This was characterized as 3,5-diiodo-4-pyridone (II) by preparation of its methyl derivative with dimethyl sulfate, m. p. 216–217°, the literature[2] reports this compound to melt at 215°.

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Summary

3,5-Diiodo-4-mercaptopyridine-S-acetic and S-β-propionic acids decompose under mild conditions to give 3,5-diiodo-4-pyridyl disulfide.

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