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HYDRAZINE DERIVATIVES. II. *ortho*-MERCAPTO-PYRIDINECARBOHYDRAZIDES

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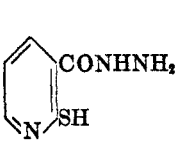
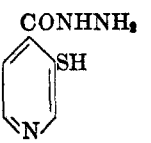
Received August 31, 1953

The significant antibacterial and antifungal activity of a series of thiosalicylhydrazides and their benzal derivatives reported in a previous communication (1) was attributed in a large part to the presence of the mercapto group contiguous to the carbohydrazido moiety. In order to further the investigation of this effect and in view of the marked activity of isonicotinyl hydrazide against *Mycobacterium tuberculosis*, the preparation of the four isomeric *o*-mercaptopyridinecarbohydrazides, I–IV, was undertaken.



I



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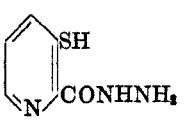
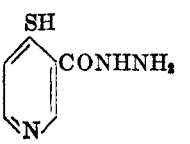


III



IV

For the preparation of I, 2-mercaptonicotinic acid (V) was prepared by the method of Sucharda and Troszkiewicz (2) from 2-aminonicotinic acid (3) by conversion to the hydroxy acid, replacement of the hydroxyl by chlorine with phosphorus pentachloride and phosphorus oxychloride, and subsequent treatment of the 2-chloronicotinic acid with sodium sulfhydrate at 130°. The esterification of this acid was unexpectedly troublesome. Fibel and Spoerri (4) had prepared the methyl ester by treatment of V with sulfuric acid and methanol, but gave no experimental details. In our hands, however, sulfuric or hydrochloric acid catalysis of this esterification gave as the sole product an ester which melted at 59–60° as compared to the 204° reported by Fibel and Spoerri.

This material did not consume iodine from a pyridine solution indicating that the mercapto moiety was no longer intact as such. Elemental analysis for carbon, hydrogen and total methyl showed that N-methylation had occurred under these relatively mild conditions to give 3-methoxycarbonyl-1-methyl-2(1*H*)-

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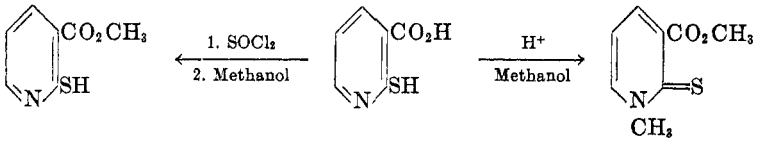
pyridinethione (VI) according to the following equation:



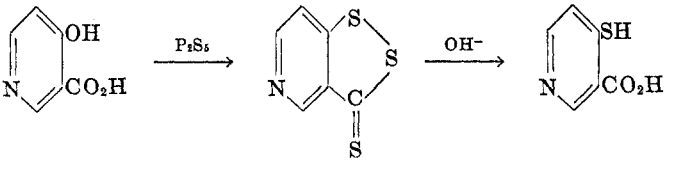
VII V VI

The desired ester VII was ultimately obtained *via* the acid chloride of V prepared with thionyl chloride and pyridine. The acid chloride was not isolated but was converted directly to the ester.

3-Mercaptoisonicotinic acid and 3-mercaptopicolinic acid necessary for the synthesis of II and III respectively were prepared by Sucharda and Troszkiewicz (2) from the requisite amino acids by diazotization and reaction of the diazonium salt with an alkaline sodium sulfide solution. In the present instance the diazonium salt was caused to react with potassium ethyl xanthate and the resulting xanthate esters upon hydrolysis yielded the disulfides, identical with the disulfides prepared by Sucharda and Troszkiewicz by oxidation of the mercapto acids. Acid-catalyzed esterification proceeded smoothly to give the disulfide diesters. Treatment of these esters with excess hydrazine hydrate reduced the disulfide linkage and replaced the ester functions to give II and III.

An attempt to prepare 4-mercaptonicotinic acid (IX) for the eventual synthesis of IV by the method employed for the 2-mercaptonicotinic acid failed. Only a small amount of starting material was recovered when 4-hydroxynicotinic acid (5) was treated with phosphorus pentachloride and phosphorus oxychloride.

The procedure of Klingsberg and Papa (6) for the conversion of 2- and 4-pyridones to the respective thiopyridones with phosphorus pentasulfide in boiling pyridine was considered worthy of investigation. Although concurrent conversion of the carboxyl group to a thiocarboxyl was expected, mild hydrolysis should have given the desired acid IX. Application of this method to 4-hydroxynicotinic acid gave a fair yield of a dark orange crystalline material, insoluble in bicarbonate and only soluble in acids and hot alkalies. Neutralization of these solutions gave back the orange crystals unchanged. Elemental analysis showed the presence of only carbon, hydrogen, nitrogen, and sulfur. An ebullioscopic molecular weight determination in acetic acid gave a value of 237.[2] On the basis

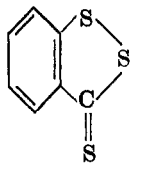


VIII IX

of the analytical results and the behavior of this material towards alkalies, structure VIII was proposed. This substance was remarkably stable to hydroly-

[2] The molecular weight of the acetate of VIII which would form in glacial acetic acid is 245.

sis, being recovered unchanged after boiling for one hour with 20% sodium hydroxide or for four hours with concentrated hydrochloric acid. Refluxing a solution in 30% sodium hydroxide for 16 hours finally gave 4-mercaptonicotinic acid (IX) upon neutralization. A search of the literature disclosed that 2,3-dithiosulfindene[3] (X) had been prepared by Mannessier (7) by heating saccharin and phosphorus pentasulfide at 225°. This substance was also reported to be excep-



X

tionally resistant to hydrolysis and in this case cleavage to thiosalicylic acid occurred only after six hours refluxing with 10% sodium hydroxide.

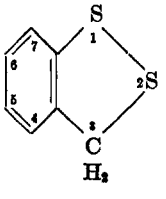
Since the tautomeric thione structure is also possible with IX, it was thought that acid-catalyzed esterification might again yield an N-methylated derivative as does V after refluxing for 7 hours with methanolic hydrogen chloride. Refluxing for 2½ hours, however, gave the "normal" ester smoothly and in good yield. In view of the comparatively small amounts of material available, no attempt was made to study the effect of a prolonged reaction time in this esterification for the purpose of effecting N-methylation.

The hydrazides were readily prepared from the esters and each in turn was condensed with 2,4-dichlorobenzaldehyde to give the respective benzal derivatives. The use of this particular aldehyde stemmed from the significant effect it had upon the antibacterial activity of other hydrazides prepared previously (1). From the microbiological data obtained to date, it is evident that none of the pyridinecarbohydrazides or their benzal derivatives are as potent fungicides or bactericides as is the benzene prototype. It is noteworthy to point out that 3-mercaptoisonicotinylhydrazide did not exhibit antitubercular activity when tested against *M-tuberculosis H37Rv* at 50 gamma/cc.

EXPERIMENTAL[4]

Methyl 2-mercaptonicotinate. To a well cooled mixture of 5 ml. of pyridine and 3 ml. of thionyl chloride was added 1.5 g. of 2-mercaptonicotinic acid in small portions so as to

[3] The Ring Index prefers the following numbering system for the parent heterocycle and VIII was named as a derivative thereof. X would then become 1,2,3-benzodithiole-3-thione in preference to the name proposed by Mannessier.



[4] All melting points are uncorrected. Microanalyses by the Clark Microanalytical Laboratory, Urbana, Illinois.

maintain the temperature below 50°. The mixture was allowed to stand for 10 minutes at room temperature and then 10 ml. of methanol was added all at once. The reaction was vigorous and had to be well cooled to keep the temperature below 50°. After the vigorous reaction was over, the solution, was warmed on the steam-bath for 10 minutes. The addition of 50 ml. of water and sufficient sodium bicarbonate to bring the solution to slight alkalinity afforded, after cooling, 1.1 g. (67.5%) of the crude ester, m.p. 185–190°, m.p. reported (4) 204°. No attempt was made to purify this material which was used directly in the subsequent reaction.

2-Mercaptonicotinylhydrazide. A solution of 1.1 g. of crude methyl 2-mercaptonicotinate in 10 ml. of ethanol and 3 ml. of hydrazine hydrate was heated on the steam-bath for 30 minutes while allowing most of the ethanol to distill off. Dilution with water and neutralization with acetic acid precipitated yellow crystals. After cooling in an ice-bath the precipitate was collected, washed with cold water, and dried at 60° to yield 1.1 g. (100%). Recrystallization from dimethylformamide-ethanol gave bright yellow crystals, m.p. 330°.

Anal. Calc'd for $C_6H_7N_3OS$: C, 42.60; H, 4.14; N, 24.85; S, 18.93.

Found: C, 42.85; H, 4.42; N, 24.46; S, 18.97.

(2,4-Dichlorobenzal)-2-mercaptonicotinylhydrazide. This derivative was prepared from the hydrazide and 2,4-dichlorobenzaldehyde in acetic acid. Recrystallization from dimethylformamide-methanol yielded yellow needles, m.p. 265–267°.

Anal. Calc'd for $C_{13}H_9Cl_2N_3OS$: C, 47.80; H, 2.76.

Found: C, 47.89; H, 2.95.

3,3'-Dithioisonicotinic acid. A solution of 26.5 g. (0.384 mole) of sodium nitrite in 125 ml. of water was added to a mixture of 53 g. (0.384 mole) of 3-aminoisonicotinic acid, 96 ml. of concentrated hydrochloric acid, and 300 ml. of water, at 0–5°. The resulting diazonium salt solution was buffered to *p*H 7.0 by the addition of solid potassium acetate and then was added in a thin stream to a well stirred solution of 100 g. of potassium ethyl xanthate in 385 ml. of water held at 60–70°. After cooling to 10° the mixture was neutralized with hydrochloric acid to give 40 g. of the xanthate ester. This material was refluxed with 13 g. of sodium hydroxide and 150 ml. of water for 1½ hours. The resulting solution was acidified with concentrated hydrochloric acid and the solid was collected and dried to yield 29 g. (49% based on amino acid), m.p. 305–308°. Sucharda (2) reported m.p. 307–308°.

Dimethyl 3,3'-dithioisonicotinate dihydrochloride. A slurry of 29 g. (0.185 mole) of the acid and 1500 ml. of methanol was refluxed for 7½ hours while passing in hydrogen chloride gas. All of the acid had dissolved after 3 hours. One liter of methanol was then distilled, and cooling the reaction mixture caused the separation of 18 g. of product. A second crop of 5 g. was obtained by dilution of the filtrate with ether. Evaporation of this filtrate left 10 g. of crude semi-solid ester. The total crude yield was 32 g. (99%). Recrystallization of crop 2 from methanol-acetone afforded light yellow needles, m.p. 166–167° dec.

Anal. Calc'd for $C_{14}H_{14}Cl_2N_2O_4S_2$: C, 41.05; H, 3.44; N, 6.84.

Found: C, 40.89; H, 3.61; N, 6.84.

Crops 1 and 3 were converted separately to the hydrazide without prior purification.

3-Mercaptoisonicotinylhydrazide. A mixture of 10 g. (0.058 mole) of crop 3 from the ester preparation and 20 ml. of hydrazine hydrate was refluxed for 3 hours. Dilution of the reaction mixture with an equal volume of water, neutralization with concentrated hydrochloric acid, and cooling in an ice-bath for ½ hour afforded 5 g. (50%) of hydrazide, m.p. 239–240°, after recrystallization from water. When treated in the same way, 17 g. of crop 1 yielded 10 g. (59%) of product.

Anal. Calc'd for $C_6H_7N_3OS$: C, 42.60; H, 4.17; N, 24.84.

Found: C, 42.76; H, 4.15; N, 24.63.

(2,4-Dichlorobenzal)-3-mercaptoisonicotinylhydrazide. To a boiling solution of 1.69 g. (0.01 mole) of 3-mercaptoisonicotinylhydrazide in a mixture of 100 ml. of methanol and 3 ml. of acetic acid was added 2.0 g. (0.012 mole) of 2,4-dichlorobenzaldehyde. Orange crystals began to separate almost immediately. After 5 minutes the mixture was chilled and the solid was separated by filtration; 2.65 g. (82%). A sample recrystallized three times from pyridine separated as orange crystals; m.p. 239–241°.

Anal. Calc'd for $C_{13}H_9Cl_2N_3OS$: C, 47.98; H, 2.75.
Found: C, 48.28; H, 2.48.

The disulfide was prepared by iodine oxidation in pyridine. The precipitate was collected and recrystallized from dimethyl formamide to yield yellow fibrous needles; m.p. 264–265°.

Anal. Calc'd for $C_{26}H_{16}Cl_4N_6O_2S_2$: C, 48.00; H, 2.48.
Found: C, 48.45; H, 2.07.

3-Mercaptopicolinic acid disulfide. 3-Aminopicolinic acid (3) (13.8 g., 0.1 mole) was dissolved in a mixture of 100 ml. of water and 25 ml. of concentrated hydrochloric acid. A solution of 6.9 g. (0.1 mole) of sodium nitrite in 40 ml. of water was added dropwise while maintaining the temperature at 0–5°. Fifteen minutes after the addition was complete, the cold solution was buffered to neutrality with solid potassium acetate and then added in a thin stream to a solution of 25 g. of potassium ethyl xanthate in 100 ml. of water maintained at 70–80°. Nitrogen evolution was vigorous and some oil separated. The mixture was cooled and treated with hydrochloric acid until no more material precipitated from the solution. The aqueous phase was decanted and the semi-solid sludge of xanthate ester was treated with 50 ml. of 5 *N* sodium hydroxide for 30 minutes on the steam-bath. Cooling and neutralization with concentrated hydrochloric acid gave a clear orange solution which was treated with an excess of copper acetate and a few milliliters of acetic acid. The dark brown copper salt was collected and washed with water. The moist cake was suspended in 200 ml. of water and 20 ml. of concentrated hydrochloric acid and was heated at the reflux while passing in hydrogen sulfide until the salt had been decomposed. After filtration the filtrate was evaporated to dryness on the steam-bath to give 7 g. of a yellow solid residue. An additional 5 g. of product was obtained by treating the aqueous phase, which had been decanted from the xanthate sludge, with copper acetate to give a green copper salt—presumably of the xanthate derivative—and subsequent decomposition as outlined above. Hydrolysis of the xanthate ester apparently occurred during the conversion of copper salt to the acid. The total yield was 12 g. (77%), m.p. 190–193°, m.p. reported (2) 206°.

Dimethyl 3,3'-dithiopicolinate. A solution of 13.5 g. (0.044 mole) of 3-mercaptopicolinic acid disulfide in 500 ml. of methanol was refluxed for 15 hours while passing in hydrogen chloride gas. The residue, after evaporating off the methanol on the steam-bath, was triturated with sodium bicarbonate solution and the insoluble ester was collected. After washing with water and drying at 50° the material, m.p. 195–200°, weighed 10.5 g. (71%). Recrystallization from methanol gave white needles; m.p. 210–212°.

Anal. Calc'd for $C_{14}H_{12}N_2O_4S_2$: C, 49.80; H, 3.82.
Found: C, 49.62; H, 3.91.

3-Mercaptopicolinylhydrazide hydrochloride. The methyl ester (12 g.) was mixed with 25 ml. of hydrazine hydrate. Heat was evolved and when the reaction slackened the mixture was refluxed for an additional 10 minutes. After cooling, the solution was diluted with 20 ml. of water and was treated with Darco. The product did not separate upon neutralization with acetic acid, but the addition of 40 ml. of concentrated hydrochloric acid and subsequent cooling caused orange platelets of the hydrochloride to separate. These were collected and washed with propanol-2 and ether to yield 4.5 g. (31%); m.p. 310°. The analytical sample was recrystallized from methanol; m.p. 310°.

Anal. Calc'd for $C_6H_8ClN_3OS$: C, 35.02; H, 3.89.
Found: C, 35.39; H, 3.93.

(2,4-Dichlorobenzal)-3-mercaptopicolinylhydrazide. This substance was prepared in essentially quantitative yield by condensing 2,4-dichlorobenzaldehyde with the hydrazide hydrochloride in aqueous alcohol and neutralization of the hydrochloric acid with sodium hydroxide. Recrystallization from pyridine-acetic acid-water gave orange crystals; m.p. 195–197°.

Anal. Calc'd for $C_{13}H_9Cl_2N_3OS$: C, 47.85; H, 2.76.
Found: C, 48.41; H, 3.07.

5-Aza-1,2,3-benzodithiole-3-thione (IV). A mixture of 2.8 g. (0.02 mole) of 4-hydroxynicotinic acid, 5.0 g. (0.022 mole) of phosphorus pentasulfide, and 30 ml. of pyridine was heated under reflux for 1½ hours. When this reaction mixture was poured into 50 ml.

of hot (70–80°) water a vigorous evolution of gases occurred and an orange-red precipitate settled out of solution. After chilling at 10° for 2 hours the solid was collected and dried at 65°; weight 1.75 g. (48%); m.p. 198–202°. A sample recrystallized from a small amount of dimethylformamide and once from pyridine separated as orange-red rhombs; m.p. 206–208°.

Anal. Calc'd for $C_6H_6NS_3$: C, 38.85; H, 1.62; N, 7.76; S, 51.90.

Found: C, 38.40; H, 1.61; N, 7.17; S, 52.23.

An ebullioscopic molecular weight determination in glacial acetic acid gave values of 237 and 238. This is in agreement with a calculated molecular weight for the acetate salt of IV of 245.

4-Mercaptonicotinic acid. 5-Aza-1,2,3-benzodithiole-3-thione (13 g., 0.070 mole), 100 g. of sodium hydroxide, and 185 ml. of water were refluxed for 16 hours. Acidification with concentrated hydrochloric acid while cooling caused the precipitation of a mixture of the product and elemental sulfur. The solid was collected and the cake was extracted with sodium bicarbonate solution. Acidification afforded 7.1 g. of light yellow mercapto acid; m.p. 235–237°. Two recrystallizations from water raised the melting point to 236–238°.

Anal. Calc'd for $C_6H_5NO_2S$: C, 46.40; H, 3.22; N, 9.01; S, 20.61.

Found: C, 46.48; H, 3.39; N, 8.84; S, 20.74.

Methyl 4-mercaptonicotinate. A mixture of 1.5 g. of 4-mercaptonicotinic acid and 20 ml. of methanol was saturated with hydrogen chloride gas at room temperature. After refluxing for 2½ hours the solution was clear and most of the methanol was then evaporated using the steam-bath. The residue was treated with water and sodium bicarbonate and the ester was collected, washed with water, and dried to yield 1.2 g. of yellow crystals, m.p. 165°. A sample recrystallized from water melted at 170–171°.

Anal. Calc'd for $C_7H_7NO_2S$: C, 49.70; H, 4.14.

Found: C, 50.03; H, 4.59.

4-Mercaptonicotinylhydrazide. This material was prepared in the same manner as the 2-mercaptonicotinylhydrazide with the exception that the solvent was omitted and the mixture was heated for only 10 minutes. From 1.0 g. of ester, 0.9 g. (90%) of hydrazide, m.p. 302–305° after softening at 230°, was obtained. Recrystallization from water gave yellow needles, m.p. 304–305° after softening at 230°. Subsequent recrystallizations did not improve the melting point.

Anal. Calc'd for $C_6H_7N_3OS$: C, 42.60; H, 4.15.

Found: C, 42.89; H, 4.37.

(2,4-Dichlorobenzal)-4-mercaptonicotinylhydrazide. Condensation of the hydrazide with 2,4-dichlorobenzaldehyde in acetic acid gave the benzal derivative, m.p. 254–255° after recrystallization from dimethylformamide-methanol.

Anal. Calc'd for $C_{13}H_9Cl_2N_3OS$: C, 47.85; H, 2.76.

Found: C, 47.68; H, 2.99.

3-Methoxycarbonyl-1-methyl-2(1H)-pyridinethione. 2-Mercaptonicotinic acid (20 g.) was dissolved in 500 ml. of methanol and the solution was refluxed for 7 hours while passing in hydrogen chloride gas. After standing at room temperature overnight the solvent was removed and the residue was dissolved in dilute hydrochloric acid. The cloudy solution was treated with Darco and filtered. The addition of sodium carbonate to the filtrate precipitated the product, which was collected, washed with water, and dried. The yield was 14 g. (59%), m.p. 50°.

Another experiment in which 6.5 g. of the acid, 1 ml. of c.p. sulfuric acid, and 200 ml. of methanol were refluxed for 18 hours gave 4 g. of ester after being treated as above. After redissolving in dilute hydrochloric acid and reprecipitation with sodium carbonate 3.3 g. (43%); m.p. 55–58° was obtained. Recrystallization from methanol gave long white needles, melting at 59–60°.

Anal. Calc'd for $C_8H_9NO_2S$: C, 52.45; H, 4.91; N, 7.65; O-methyl, 16.95; N-methyl, 8.19.

Found: C, 52.40; H, 4.95; N, 7.31; O-methyl, 17.36; N-methyl, 8.18.

It is noteworthy to point out that an attempt to prepare methyl 2-mercaptonicotinate with excess diazomethane resulted in a 75% yield of the same N-methylated compound.

3-Carbohydrazido 1-methyl-2(1H)-pyridinethione. A solution of 14 g. of ester and 15 ml. of hydrazine hydrate was allowed to stand overnight at room temperature. The mixture had set to a thick mass of crystals by this time. After refluxing for 1 hour the excess hydrazine hydrate was removed at 100° under a water pump vacuum. The residue was dissolved in 30 ml. of hot water and 8 ml. of acetic acid was added. Cooling deposited crystals of the hydrazide. The material was collected, washed with a small quantity of water, and dried to yield 7.8 g. (56%); m.p. 130–133°. Three recrystallizations from ethylene chloride-petroleum ether gave white feathery needles; m.p. 141–142°.

Anal. Calc'd for $C_7H_9N_3OS$: C, 45.85; H, 4.91.

Found: C, 45.73; H, 5.03.

3-(2,4-Dichlorobenzal)carbohydrazido-1-methyl-2(1H)-pyridinethione. Condensation of the hydrazide with 2,4-dichlorobenzaldehyde in methanol gave light yellow needles; m.p. 204–205°. Additional recrystallizations from methanol did not raise the melting point.

Anal. Calc'd for $C_{14}H_{11}Cl_2N_3OS$: C, 49.41; H, 3.23.

Found: C, 49.98; H, 3.63.

SUMMARY

The preparation of the four isomeric *o*-mercaptopyridinecarbohydrazides from the respective esters has been described.

Acid-catalyzed esterification of 2-mercaptonicotinic acid for 7–15 hours gave good yields of 3-methoxycarbonyl-methyl-2(1*H*)-pyridinethione (VI).

Treatment of 4-hydroxynicotinic acid with phosphorus pentasulfide in pyridine produced 5-aza-1,2,3-benzodithiole-3-thione (VIII), which was converted to 4-mercaptonicotinic acid by drastic alkaline hydrolysis.

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