reaction solution. After the reaction ceased the precipitate was filtered, recrystallized from larger amounts of chloroform, and 1,9-dihydroxyphenazine 5-mono-N-oxide (XVIII) was obtained as red plates of m.p. 258° (decomp.). The filtrate was washed with water, shaken with sodium hydroxide, and the alkaline solution was neutralized with acetic acid. From the precipitate thus obtained only 1,9-dihydroxyphenazine 5-mono-N-oxide was purified. Prolonged oxidation produced a smaller yield. Mono-N-oxide dissolved in alkaline solution with violet coloration. *Anal.* Calcd. for $C_{12}H_8O_3N_2$; C, 63.15; H, 3.50; N, 12.28. Found: C, 63.00; H, 3.54; N, 11.96.

N-Oxidation of 2,8-Diacetoxyphenazine—2,8-Diacetoxyphenazine (0.2 g.) was dissolved in benzene (130 cc.) and oxidized with hydrogen peroxide (3.5 cc.) and acetic anhydride (3 cc.) for 7 hours on water bath. After the reaction ceased, the benzene solution was shaken with 10% sodium hydroxide. From the benzene layer, orange-red prisms (from benzene), m.p. 195~197°, were obtained, which were saponified with sodium hydroxide solution, and after neutralizing with acetic acid, orange-red microcrystals (from a large amount of ethanol), m.p. over 310°, were obtained. Red coloration was produced in sodium hydroxide solution. *Anal.* Found: C, 63.36; H, 3.75.

Summary

1,7-, 1,9-, and 2,8-dihydroxyphenazines were synthesized by the improved Wohl-Aue method. From 1,7-dihydroxyphenazine, 1,7-dihydroxyphenazine di-N-oxide was obtained by oxidation with hydrogen peroxide and acetic anhydride in benzene solution.

In the case of the 1,9-isomer, only its mono-N-oxide was obtained by the same oxidation condition employed for the 1,7-isomer.

The oxidation product of 2,8-dihydroxyphenazine, however, agreed neither with the di-N-oxide nor with mono-N-oxide.

(Received November 7, 1954)

---

8. **Torizo Takahashi, Juichiro Shibasaki, and Masao Uchibayashi:**

Syntheses of Heterocyclic Compounds of Nitrogen. LXXXVIII*. Phenyl Pyridyl Ethers. (8)**.

(*Pharmaceutical Institute, Medical Faculty, University of Tokyo****)

In the previous papers of this series, we reported on the syntheses of several kinds of phenyl pyridyl ethers, with a view to examining their antitubercular activities. The present paper describes the synthesis of derivatives possessing a thioether linkage in the γ-position of pyridine.

For the preparation of the starting material, γ-thiopyridone, the method described by Koenigs and his co-worker¹⁾ appeared inconvenient as it gave this compound in poor yield by the treatment of unstable γ-chloropyridine in ethanol as solvent with potassium hydrogen sulfide in a sealed tube. For this reason, the method of King and his co-worker²⁾ was followed converting chelidonic acid³⁾ into γ-pyridone and treating the latter with phosphorus pentasulfide. In the present case, however, the reaction temperature in the latter step was required to be raised up to approximately 150°, while the temperature range reported by King was 60~70°.

---

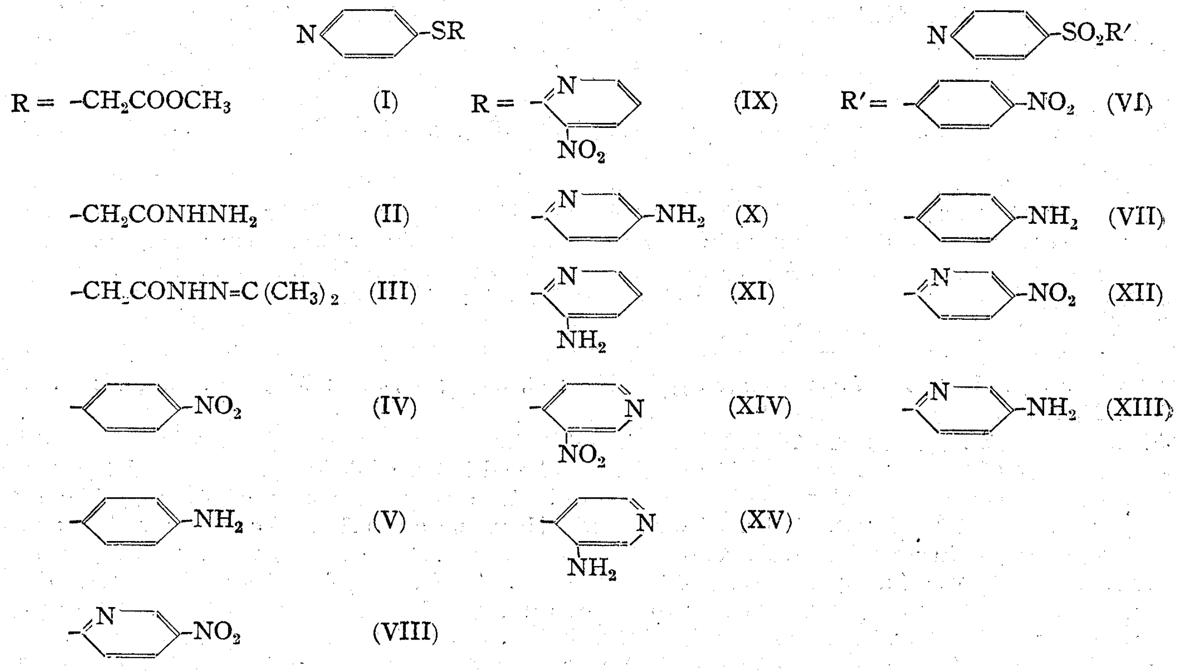
* Part LXXXVII: J. Pharm. Soc. Japan, 73, 1078 (1953).
** Part (7): This Bulletin, 1, 70 (1953).
*** Yoshida-Konoe-cho, Sakyo-ku, Kyoto (高橋酉蔵, 柴崎寿一郎, 内林政夫).
1) Koenigs, Kinne: Ber., 54, 1357 (1921).
2) King, Ware: J. Chem. Soc., 1939, 873.
3) Gilman: Org. Syntheses, 17, 40 (1937).

Pyridyl-(4)-thioacetic acid hydrazide was first prepared, as a compound having the structure analogous to that of isonicotinic acid hydrazide, in the following manner. γ-Thiopyridone was allowed to condense with methyl monochloroacetate to form methyl pyridyl-(4)-thioacetate (I), which was converted by the action of hydrazine hydrate into its hydrazide (II). (II), when treated with acetone at a room temperature, furnished acetone pyridyl-(4)-thioacetylhydrazone (III).

The condensation of the potassium salt of γ-thiopyridone with *p*-nitrochlorobenzene was effected by heating in the presence of copper powder at 180~200° for three hours, and gave 4-nitrophenyl pyridyl-(4′) thioether (IV), which on reduction with ammonium chloride and iron powder, led to 4-aminophenyl pyridyl-(4′) thioether (V). (IV), on oxidation with potassium permanganate in dilute acetic acid, yielded 4-nitrophenyl pyridyl-(4) sulfone (VI), which in turn was reduced with ammonium chloride and iron powder to 4-aminophenyl pyridyl-(4′) sulfone (VII).

The cendensation of the potassium salt of γ-thiopyridone with 2-chloro-5-nitropyridine[4] and 2-chloro-3-nitropyridine[5] proceeded on heating in ethanol for about ten minutes to form 5-nitrodipyridyl-(2,4′) thioether (VIII) and 3-nitrodipyridyl-(2,4′) thioether (IX), respectively. (VIII) and (IX), on reduction with stannous chloride and hydrochloric acid, furnished 5-aminodipyridyl-(2,4′) thioether (X) and 3-aminodipyridyl-(2,4′) thioether (XI), respectively. The oxidation of (VIII) with potassium permanganate in dilute acetic acid gave 5-nitrodipyridyl-(2,4′) sulfone (XII), which on reduction with ammonium chloride and iron powder, led to 5-aminodipyridyl-(2,4′) sulfone (XIII).

The condensation of the potassium salt of γ-thiopyridone with 3-nitro-4-chloropyridine hydrochloride[6] to form 3-nitrodipyridyl-(4,4′) thioether (XIV) was achieved in dioxane-water at room temperature, and in ethanol, instead of the above solvent, the reaction resulted in the formation mainly of 3-nitro-4-ethoxypyridine[7]. On reduction with ammonium chloride and iron powder, (XIV) was led to 3-aminodipyridyl-(4,4′) thioether (XV).



---

4) Caldwell, Korufeld: J. Am. Chem. Soc., 64, 1697 (1942).
5) Saikachi, Takahashi: J. Pharm. Soc. Japan, 64, 201 (1944).
6) Koenigs, Fulde: Ber., 60, 2106 (1927).
7) Koenigs, Freter: *Ibid.*, 57, 1187 (1921).

The antitubercular activities of the compounds reported in the previous paper (Part LXXVII[8]) and in this paper were tested *in vitro* by Prof. S. Mori and Assist.-Prof. T. Yamori of the Pathological Laboratory of the Medical Faculty, University of Kyoto, with the results given in Table I. The samples used were dissolved in propylene glycol and tested on human type tubercle bacilli in Kirchner's nutrient medium.

TABLE I.

Compound	Dilution of growth inhibition
Pyridyl-(4)-thioacetic acid hydrazide (II)	1 : 20,000
4-Aminophenyl pyridyl-(4′) thioether (V)	1 : 20,000
4-Aminophenyl pyridyl-(4′) sulfone (VII)	1 : 5,000
5-Aminodipyridyl-(2,4′) sulfone (XIII) (hydrochloride)	1 : 5,000
3-Aminodipyridyl-(4,4′) thioether (XV)	1 : 10,000
4-Chlorophenyl 5′-aminopyridyl-(2′) thioether	1 : 5,000
2,5-Dichlorophenyl 5′-aminopyridyl-(2′) thioether	1 : 10,000
Phenyl 3-aminopyridyl-(2) thioether	1 : 5 000
4-Aminophenyl 3′-aminopyridyl-(2′) thioether	1 : 2,000
4-Chlorophenyl 3′-aminopyridyl-(2′) thioether	1 : 2,000
2,5-Dichlorophenyl 3′-aminopyridyl-(2′) thioether	1 : 10,000
Phenyl 3-chloro-5-aminopyridyl-(2) thioether	1 : 160,000
2,5-Dichlorophenyl 3′-chloro-5′-aminopyridyl-(2′) thioether	1 : 5,000
4-Aminophenyl 2′-aminopyridyl-(5′) thioether	1 : 5,000
4-Chlorophenyl 2′-aminopyridyl-(5′) thioether	1 : 10,000
2,5-Dichlorophenyl 2′-aminopyridyl-(5′) thioether	1 : 20,000

This work has been supported by a grant from the Ministry of Education to which we are greatly indebted.

Experimental

Methyl Pyridyl-(4) Thioacetate (I)—To a suspension of 0.5 g. of 4-thiopyridone in 5 cc. of water was added 0.5 g. of methyl monochloroacetate and the mixture was heated on a boiling water bath until solution was complete (about an hour). The cooled reaction mixture was neutralized with anhydrous sodium carbonate, extracted with ether, and the ether extract was dried over anhydrous sodium sulfate. Removal of the solvent yielded 0.69 g. of crude (I), m.p. 26∼34°. This product was used as material for the following experiments without purification.

Pyridyl-(4) Thioacetic Acid Hydrazide (II)—A mixture of 0.4 g. of crude (I) in 0.4 g. of hydrazine hydrate was heated at 95∼100° for 2 hours. From the resulting solution, the excess hydrazine hydrate was removed under a reduced pressure and the oily product soon solidified. Recrystallization from ethanol yielded 0.17 g. of colorless pillars, m.p. 105∼107°. *Anal.* Calcd. for $C_7H_9ON_3S$: C, 45.90; H, 4.92; N, 22.95. Found: C, 45.67; H, 4.60; N, 22.84.

Acetone Pyridyl-(4) Thioacetylhydrazone (III)—0.2 g. of (II) was dissolved in 1 cc. of acetone and after standing overnight crystals appeared. Recrystallization from ethanol gave 0.15 g. of colorless needles, m.p. 140°. *Anal.* Calcd. for $C_{10}H_{13}ON_3S$: C, 53.81; H, 5.83; N, 18.83. Found: C, 53.89; H. 6.08; N, 18.43.

4-Nitrophenyl Pyridyl-(4′) Thioether (IV)—To a solution of 0.6 g. of potassium hydroxide in a small amount of water were added 10 cc. of ethanol and 1.2 g. of 4-thiopyridone, and the solution was evaporated to dryness under a reduced pressure. The potassium salt of 4-thiopyridone thus obtained was mixed well with 1.5 g. of *p*-chloronitrobenzene and 0.1 g. of copper powder and the mixture was heated in an oil bath at 180∼200° for 3 hours. After cooling, water was added to the reaction mixture to wash away unreacted 4-thiopyridone. The remainder was acidified with diluted hydrochloric acid and extracted with ether to remove unreacted *p*-chloronitrobenzene. The aqueous layer was made alkaline with sodium hydroxide solution, the precipitate was filtered, washed with water, and dried. The crude product (1.0 g.) was recrystallized from benzene-petroleum ether to yellow prisms, m.p. 75∼77°. *Anal.* Calcd. for $C_{11}H_8O_2N_2S$; C, 56.90; H. 3.45; N, 12.07. Found: C, 56.98; H, 3.43; N, 12.28.

---

8) Takahashi, Shibasaki: J. Pharm. Soc. Japan, 72, 1141 (1952).

4-Aminophenyl Pyridyl-(4′) Thioether (V)—To a mixture of 0.4 g. of ammonium chloride, 2.6 g. of iron powder, and 25 cc. of water, was added 1.0 g. of (IV). The mixture was stirred and heated at 80~85° during the addition of (IV) and for 2 hours thereafter. After cooling, the insoluble product was filtered, washed with water, dried, and extracted with ethyl acetate. Removal of the solvent yielded a residue (0.6 g.) which was recrystallized from benzene to pale yellow scales, m.p. 169~171°. *Anal.* Calcd. for $C_{11}H_{10}N_2S$: C, 65.35; H, 4.95. Found: C, 65.71; H, 4.91.

4-Nitrophenyl Pyridyl-(4′) Sulfone (VI)—To a solution of 1.65 g. of (IV) in 60 cc. of 20% acetic acid was added dropwise a saturated aqueous solution of 5.5 g. of potassium permanganate with stirring at room temperature until the color of permanganate disappeared. After continued stirring for an hour, 30% aqueous hydrogen peroxide solution was added slowly to the reaction mixture to dissolve the resulting precipitate of manganese dioxide. Crystals in the reactant were collected, washed with water, and dried. The crude product (1.05 g.) was recrystallized from benzene to colorless needles, m.p. 148~150°. *Anal.* Calcd. for $C_{11}H_8O_4N_2S$: C, 50.00; H, 3.03. Found: C, 50.13; H, 3.02.

4-Aminophenyl Pyridyl-(4′) Sulfone (VII)—Three-tenths gram of ammonium chloride, 2.0 g. of iron powder, 20 cc. of water, and 0.65 g. of (VI) were treated in the same way as in the case of (V). The dried insoluble product was extracted with acetone and removal of the solvent gave a residue (0.35 g.) which was recrystallized from ethanol to pale yellow needles, m.p. 259° (decomp.). *Anal.* Calcd. for $C_{11}H_{10}O_2N_2S$: C, 56.41; H, 4.27. Found: C, 56.67; H, 4.16.

5-Nitrodipyridyl-(2,4′) Thioether (VIII)—To a solution of 0.3 g. of potassium hydroxide in a small amount of water and 7 cc. of ethanol were added consecutively 0.55 g. of 4-thiopyridone, 0.75 g. of 2-chloro-5-nitropyridine, and 0.1 g. of copper powder in turn. The mixture was heated on a water bath for about 10 minutes and filtered while warm to remove the depositing potassium chloride, and the filtrate was concentrated to a small volume. After standing, crystals were collected and dried. The crude product (1.1 g.) was recrystallized from ethanol to yellow needles, m.p. 90~92°. *Anal.* Calcd. for $C_{10}H_7O_2N_3S$: C, 51.50; H, 3.00. Found: C, 51.75; H, 2.95.

3-Nitrodipyridyl-(2,4′) Thioether (IX)—To a solution of 0.3 g. of potassium hydroxide in a small amount of water and 7 cc. of ethanol were added consecutively 0.46 g. of 4-thiopyridone, 0.62 g. of 2-chloro-3-nitropyridine, and 0.1 g. of copper powder. The treatment of the mixture was made in the same way as in the case of (VIII). The crude product (0.83 g.) was recrystallized from ethanol to yellow plates, m.p. 153~154°. *Anal.* Calcd. for $C_{10}H_7O_2N_3S$: C, 51.50; H, 3.00; N, 18.03. Found: C, 51.68; H, 3.08; N, 18.18.

5-Aminodipyridyl-(2,4′) Thioether (X)—Addition of 0.7 g. of (VIII) to a solution of 6.0 g. of stannous chloride in 6 cc. of concentrated hydrochloric acid resulted in an almost clear solution with rise of temperature. The reaction mixture was heated on a boiling water bath for 2 hours and then evaporated to dryness under a reduced pressure. The residue was made strongly alkaline with 30% aqueous sodium hydroxide and extracted with ether, which was dried over anhydrous sodium sulfate and evaporated. Recrystallization of the residue from ether yielded 0.11 g. of colorless scales, m.p. 153~155°. *Anal.* Calcd. for $C_{10}H_9N_3S$: C, 59.11; H, 4.43. Found: C, 59.21; H, 4.44.

3-Aminodipyridyl-(2,4′) Thioether (XI)—Three g. of stannous chloride, 3 cc. of concentrated hydrochloric acid, and 0.4 g. of (IX) were treated in the same way as in the case of (X). The crude product, thus obtained was recrystallized from petroleum ether to give 0.08 g. of colorless scales, m.p. 89~92°. *Anal.* Calcd. for $C_{10}H_9N_3S$: N, 20.69. Found: N, 21.22.

5-Nitrodipyridyl-(2,4′) Sulfone (XII)—A suspension of 2.34 g. of (VIII) in 100 cc. of 20% acetic acid and a saturated aqueous solution of 6.0 g. of potassium permanganate were treated in the same way as in the case of (VI). Recrystallization from benzene yielded 1.12 g. of colorless needles, m.p. 167~169°. *Anal.* Calcd. for $C_{10}H_7O_4N_3S$: C ,45.28; H, 2.64; N, 15.85. Found: C, 45.02; H, 2.62; N, 15.89.

5-Aminodipyridyl-(2,4′) Sulfone (XIII)—To a mixture of 0.3 g. of ammonium chloride, 2.0 g. of iron powder, and 25 cc. of water, was added 1.0 g. of (XII) in small portions. The mixture was stirred and heated at 80~85° during the addition of (XII) and for an hour thereafter. After cooling, the insoluble product was filtered, dried, and extracted with acetone. Removal of the solvent yielded a residue (0.45 g.) which was recrystallized from hot water to colorless needles, m.p. 196~198°. *Anal.* Calcd. for $C_{10}H_9O_2N_3S$: C, 51.06; H, 3.83; N, 17.87. Found: C, 51.27; H, 3.88; N, 18.19.

3-Nitrodipyridyl-(4,4′) Thioether (XIV)—To a solution of 0.6 g. of potassium hydroxide in 4 cc. of water were added consecutively 0.65 g. of 4-thiopyridone, 6 cc. of dioxane, and 1.0 g. of 3-nitro-4-chloropyridine hydrochloride. The solution soon turned red and potassium chloride deposited. After continued stirring for 2 hours at a room temperature, the reaction mixture was filtered and the filtrate concentrated under a reduced pressure. The residue was washed with water and dried. Recrystallization of the crude product (1.05 g.) from benzene-petroleum ether yielded yellow needles, m.p. 114.5~116°. *Anal.* Calcd. for $C_{10}H_7O_2N_3S$: C, 51.50; H, 3.00; N, 18.03. Found: C, 51.65; H, 3.05; N, 18.22.

3-Aminodipyridyl-(4,4′) Thioether (XV)—Three-tenths gram of ammonium chloride, 2.0 g.

of iron powder, 25 cc. of water, and 0.75 g. of (XIV) were treated in the same way as in the case of (XIII). Removal of acetone left an oil which was converted to its crystalline hydrochloride (0.17 g.) by treatment with concentrated hydrochloric acid. Recrystallization from methanol yielded yellow needles, m.p. above 300°. *Anal.* Calcd. for $C_{10}H_9N_3S \cdot HCl$: C, 50.10; H, 4.18; N, 17.54. Found: C, 50.20; H, 4.33, N, 16.76.

Summary

The preparations of several pyridyl-(4) thioethers and pyridyl-(4) sulfone were described, along with some of their antitubercular activities *in vitro*.

(Received November 30, 1953)

---

9. **Torizo Takahashi and Kan-ichi Ueda:** Sulfur-containining Pyridine Derivatives. XXXIX.* Behaviour of 3-Nitro-4-thiocyanopyridine and Synthesis of 2′-Aminopyrido-3,4 : 4′,5′-thiazole and Related Compounds.

(*Pharmaceutical Institute, Medical Facutly, University of Kyoto***)

Koenigs and his co-workers have already reported on two occasions about the synthesis of 3-nitro-4-chloropyridine. In one of them Koenigs and Freter[1] stated that they prepared 3-nitro-4-chloropyridine as a crude product for the purpose of determining the position of the nitro group in the nitro compound obtained from nitration of 4-hydroxypyridine, but later Bremer[2] pointed out that the above-mentioned chloro compound should be 3-nitro-4-ethoxypyridine hydrochloride and not 3-nitro-4-chloropyridine. On the other hand, Koenigs and Fulde[3] prepared 3-nitro-4-chloropyridine hydrochloride (II) by heating 3-nitro-4-hydroxypyridine (I) with phosphorus pentachloride and phosphoryl chloride, and treating the reaction mixture with chloroform. This time, by means of Koenigs and Fulde's method, the same product described in the report was obtained.

Also, the free base (III), m.p. 45°, was obtained from (II) by Reitmann[4], but the authors obtained (III) by adding potassium acetate into the glacial acetic acid solution of (II), and the melting temperature was 29~30°.

On standing for a few days, (III) underwent a slow change to a colored matter which changes to red color on the addition of a drop of caustic alkali solution.

This color reaction is similar to that of 2,4-dinitrophenylpyridinium chloride produced by the polymerization of pyridine and 2,4-dinitro-1-chlorobenzene, and also, from the structure of (III), the formation of (IV) and, moreover, that of the product made by several molecules of (III) would be expected.

3-Nitro-4-chloropyridine hydrochloride reacting with potassium acetate and potassium thiocyanide in glacial acetic acid at room temperature produced 3-nitro-4-thiocyanopyridine (V) in excellent yield. When the reaction was carried out while heating

---

* Part XXXVIII: J. Pharm. Soc. Japan, 73, 442 (1953).

** Yoshida-konoe-cho, Sakyo-ku, Kyoto (高橋酉蔵, 上田寛一).

[1] Koenigs, Freter: Ber., 57, 1189 (1924).

[2] Bremer: Ann., 529, 290 (1937).

[3] Koenigs, Fulde: Ber., 60, 2107 (1927).

[4] Reitmann: Abhandlungen aus den Forshungsstatten der I. G. Farbenindustrie A.-G. Bd. II, 387; (cf. Ann., 521, 291 (1936)).