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*.

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## 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.

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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

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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)).

on a water bath, compound (V) was not obtained but another compound, yellow needles, m.p. 200°, was produced which showed no melting point depression on admixture with 3-nitro-4-aminopyridine[5], m.p. 200°, proving it to be undoubtedly 3-nitro-4-aminopyridine (VI). Futhermore, reaction of 3-nitro-4-aminopyridine with acetic anhyride produced 3-nitro-4-acetaminopyridine (VII).

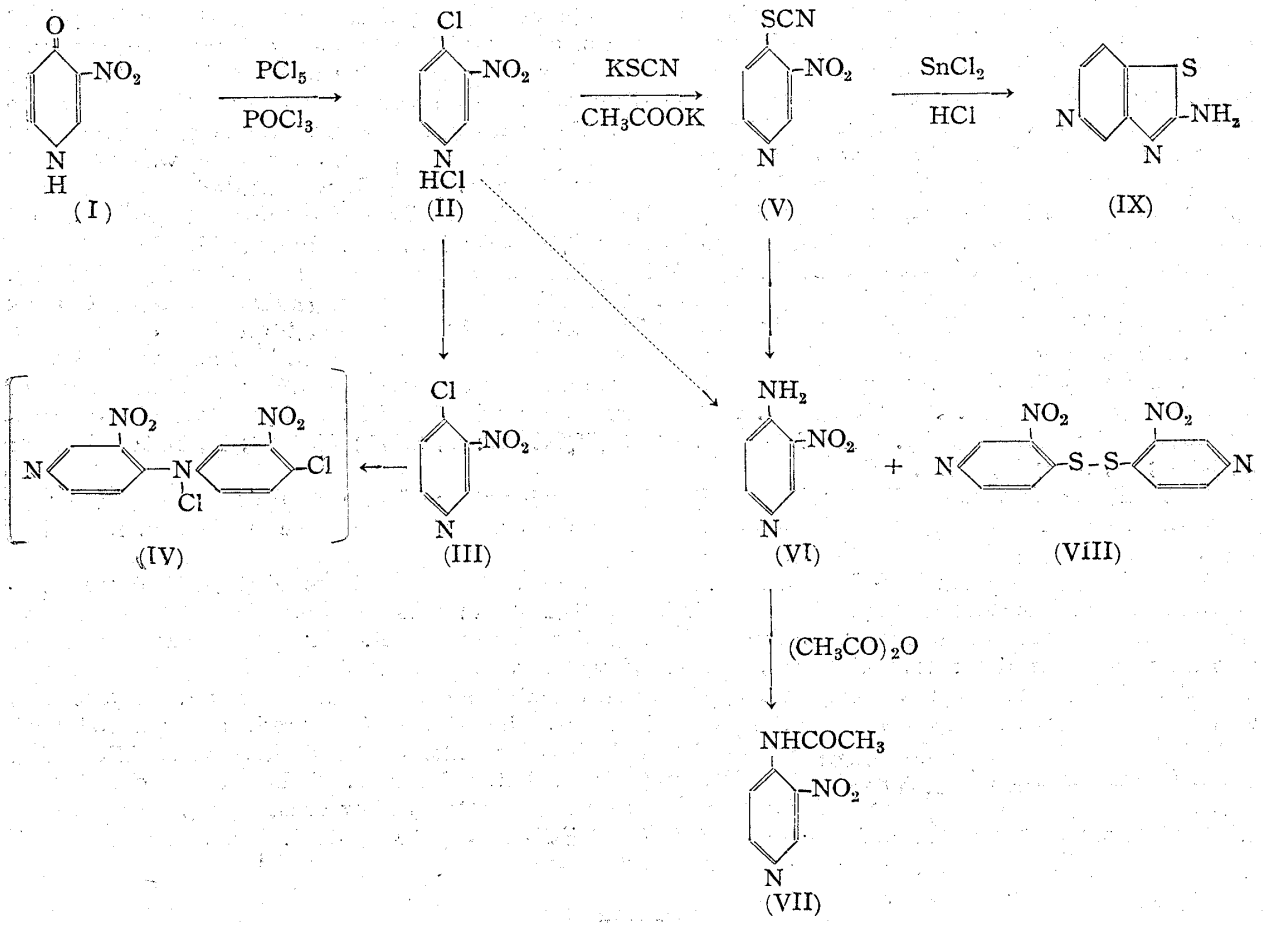
On the other hand, when (V) was heated with glacial acetic acid on a water bath, (VI) was obtained, but in this case, small amount of a product, m.p. 233° (decomp.), was produced. The latter was found by analysis to be 3,3′-dinitrodipyridyl 4,4′-disulfide (VIII).

Judging from the results obtained, it was determined that the change from (II) to (VI) is a change (II)→(V)→(VI), that is, a secondary change of thiocyano radical. This behaviour of the thiocyano radical of (V) to change to the amino group is considered to be of great interest.

In regard to the mechanism of the above-mentioned change, further report will be made at another opportunity.

2′-Aminopyrido-3,4 : 4′,5′-thiazole (IX) was prepared from (V) by the action of stannous chloride and hydrochloric acid. Its chloroaurate, which decomposed at 265°, was found by analysis to have the following composition : $C_6H_5N_3S \cdot 2HCl \cdot 2AuCl_3$.

The authors wish to acknowlege with thanks that a part of the expenses for this research was furnished by the Scientific Research Fund provided by the Ministry of Education.




5) Koenings, Mields, Gurlt: Ber., 57, 1183 (1924).

## Experimental

**3-Nitro-4-chloropyridine (III)**—To a mixture of 5 g. of 3-nitro-4-hydroxypyridine and 8 g. of phosphorus pentachloride were added several drops of phosphoryl chloride, keeping the mixture at 120°. After a vigorous reaction and evolution of hydrochloric acid gas was observed, the contents slowly liquified. After being cooled, two volumes of chloroform was added into the mixture and 3-nitro-4-chloropyridine hydrochloride (II) separated out and was rapidly collected by filtration. When a mixture of chloroform and alcohol was added into the filtrate under cooling, further separation of (II) developed. Recrystallization from ethyl acetate yielded 4.5 g. of prisms, m.p. 156° (decomp.). The melting point coincided with that in the literature[3].

Above-mentioned hydrochloride (II) was dissolved in glacial acetic acid and potassium acetate was added into the solution. Potassium chloride thereby produced was removed by filtration. The filtrate was diluted with water, neutralised with solid sodium carbonate, and the dark brown precipitated solid filtered. The precipitated solid was extracted with ethyl acetate after which the ethyl acetate was distilled off, leaving an oily residue which soon solidified. Recrystallization from a mixture of ether and petroleum ether yielded colorless needles, m.p. 29~30°. *Anal.* Calcd. for $C_5H_3O_2N_2Cl$: C, 37.88; H, 1.89. Found: C, 37.96; H, 1.95.

**3-Nitro-4-thiocyanopyridine (V)**—To the solution of 5 g. of (II) in 32 cc. of glacial acetic acid was added 2.5 g. of potassium acetate, on which potassium chloride separated out. Further, 4 g. of potassium thiocyanate was added to the solution without removing the potassium chloride. The reaction advanced exothermally and was allowed to stand at a room temperature, with occasional shaking, for five hours. The mixture was diluted with three volumes of water. The precipitate which formed was filtered and washed with water. After being dried, the precipitate was recrystallized from benzene and formed colorless prisms, m.p. 139°. On the other hand, when the filtrate was neutralised with solid sodium carbonate, (V) was obtained. The yield was quantitative. *Anal.* Calcd. for $C_6H_3O_2N_3S$: C, 39.77; H, 1.66; N, 23.20. Found: C, 39.54; H, 1.80; N, 23.16.

**3-Nitro-4-aminopyridine (VI)**—To a solution of 2 g. of 3-nitro-4-chloropyridine hydrochloride in 15 cc. of glacial acetic acid, 1 g. of potassium acetate and 3 g. of potassium thiocyanate were added and the mixture heated on a water bath for two hours, after which potassium chloride was removed by filtration and the filtrate diluted with water. Small amounts of solids separated out. The solid was removed by filtration and the filtrate neutralised with solid sodium carbonate. The precipitate was separated out, filtered, and washed with water. After being dried, recrystallization from ethyl acetate produced 1 g. of yellow needles, m.p. 200°. No melting point depression was observed when mixed with 3-nitro-4-aminopyridine (VI). Futhermore, when (VI) was heated with excessive acetic anhydride, 3-nitro-4-acetaminopyridine (VII) was obtained. Recrystallization from methanol yielded colorless prisms, m.p. 115°. *Anal.* Calcd. for $C_7H_7O_3N_3$: N, 23.20. Found: N, 23.03.

**Reaction of (V) with Glacial Acetic Acid**—To 10 cc. of glacial acetic acid was added 1 g. of (V) and heated on a water bath for 2 hours. The color of the solution gradually changed to dark red. After being heated, the content was diluted with 30 cc. of water and allowed to stand for a while. The precipitate thereby obtained was collected by means of filtration, and washed with water. After being dried, recrystallization from a mixture of dioxane and ether yielded 0.2 g. of pale yellow prisms, m.p. 233° (decomp.). This substance was found by analysis to be 3,3′-dinitrodipridyl 4,4′-disulfide (VIII). *Anal.* Calcd. for $C_{10}H_6O_2N_4S_2$: C, 38.71; H, 1.93; N, 18.06. Found: C, 38.93; H, 2.20; N, 18.19.

The filtrate was neutralised with solid sodium carbonate and the resulting precipitate was filtered. After recrystallization from ethyl acetate the compound which weighed 0.5 g. melted at 200°. No melting point depression was observed when mixed with (VI).

**2′-Aminopyrido-3,4 : 4′,5′-thiazole (IX)**—22.4 g. of stannous chloride ($SnCl_2 \cdot 2H_2O$) was dissolved in 40 g. of concentrated hyrochloric acid. When 3 g. of (V) was added to the solution in small portions an exothermal reaction was observed and solids separated out. After the reaction mixture was allowed to stand for several hours, 500 cc. of water was added. Hydrogen sulfide gas was passed into this solution, the precipitate filtered, and the filtrate evaporated in vacuum. The residue was neutralised with diluted ammonium hydroxide, precipitated solids filtered, and washed with water. Recrystallization from alcohol yielded colorless crystals, m.p. 296° (decomp.). Yield, 2 g. *Anal.* Calcd. for $C_6H_5N_3S$: C, 47.66; H, 3.31. Found: C, 47.63; H, 3.47. When auric chloride in water was added to the dilute hydrochloric acid solution of (IX), yellow crystals, which decomposed at 265°, were obtained. *Anal.* Calcd. for $C_6H_5N_3S \cdot 2HCl \cdot 2AuCl_3$: Au, 47.45. Found: Au, 47.12.

## Summary

3-Nitro-4-chloropyridine hydrochloride was converted in almost quantitative yields to 3-nitro-4-thiocyanopyridine, and 3-nitro-4-thiocyanopyridine was allowed to react with

stannous chloride in concentrated hydrochloric acid to produce 2′-aminopyrido-3,4 : 4′,5′-thiazole. When 3-nitro-4-thiocyanopyridine was heated with glacial acetic acid, 3-nitro-4-aminopyridine was obtained. The change of the thiocyano radical of 3-nitro-4-thiocyanopyridine to the amino group is considered to be of great interest.

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## 10. Shigehiko Sugasawa, Takashi Tatsuno, and Takashi Kamiya: A Synthesis of *rac*-4-(N-methylpyrrolid-2′-yl)-pyridine.

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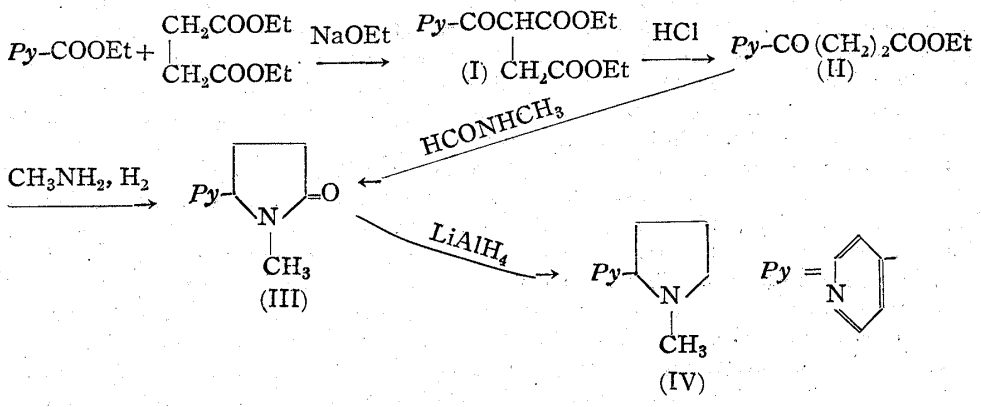
In connection with other synthetical works now going on in our hands, we needed 4-(N-methylpyrrolid-2′-yl)-pyridine (*rac*-γ-nicotine) as one of the starting materials, whose synthesis is not described in any literature.

Our first attempt to prepare this compound according to Späth's synthesis[1] of *rac*-nicotine ended fruitless but the synthesis by the following scheme turned out to be successful.




Ethyl isonicotinate was condensed with diethyl succinate by means of sodium ethoxide, giving diethyl isonicotinoylsuccinate (I) in 40~50% yield. The latter was hydrolyzed by boiling with dilute hydrochloric acid, followed by esterification, yielding ethyl β-isonicotinoylpropionate (II) in 25~30% yield. This was then subjected to hydrogenation in the presence of methylamine over Raney nickel under pressure,[2] yielding 5-(pyrid-4′-yl)-1-methylpyrrolid-2-one (III) in a fair yield. The latter was then reduced with lithium aluminum hydride preferably in tetrahydrofuran[3] to give the ultimate product (IV) in excellent yield.

*rac*-γ-Nicotine thus prepared comes as colorless liquid with an odor like that of natural nicotine. It forms crystalline *l*-γ-nicotine *d*-tartrate, when treated with *d*-tartaric acid and physiological properties of this salt is now being investigated.

The authors' thanks are due to members of the analysis room of this Institute for microanalytical data.

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1) Späth, *el al.*: Ber., 61, 327 (1928).
2) cf. Org. Syntheses, 27, 28.
3) Moffet, White: J. Org. Chem., 17, 407 (1952).