untersucht. Auch 4-Pyridon-silbersalz lieferte durch Einwirkung von Phenacylbromid in Äthanol N-Phenacyl-4-pyridon.

(Eingegangen am 21. Februar, 1958)

UDC 547.825.07

67. Torizo Takahashi and Yoshifumi Maki : Sulfur-containing Pyridine Derivatives. LVI.* Smiles Rearrangement of Pyridine Derivatives and Synthesis of Benzopyrido- and Dipyrido-1,4-thiazine Derivatives. (4).

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In the previous papers,*,[1] it was shown from results of examining reaction conditions that pyridine derivatives suffered easier Smiles rearrangement than benzene

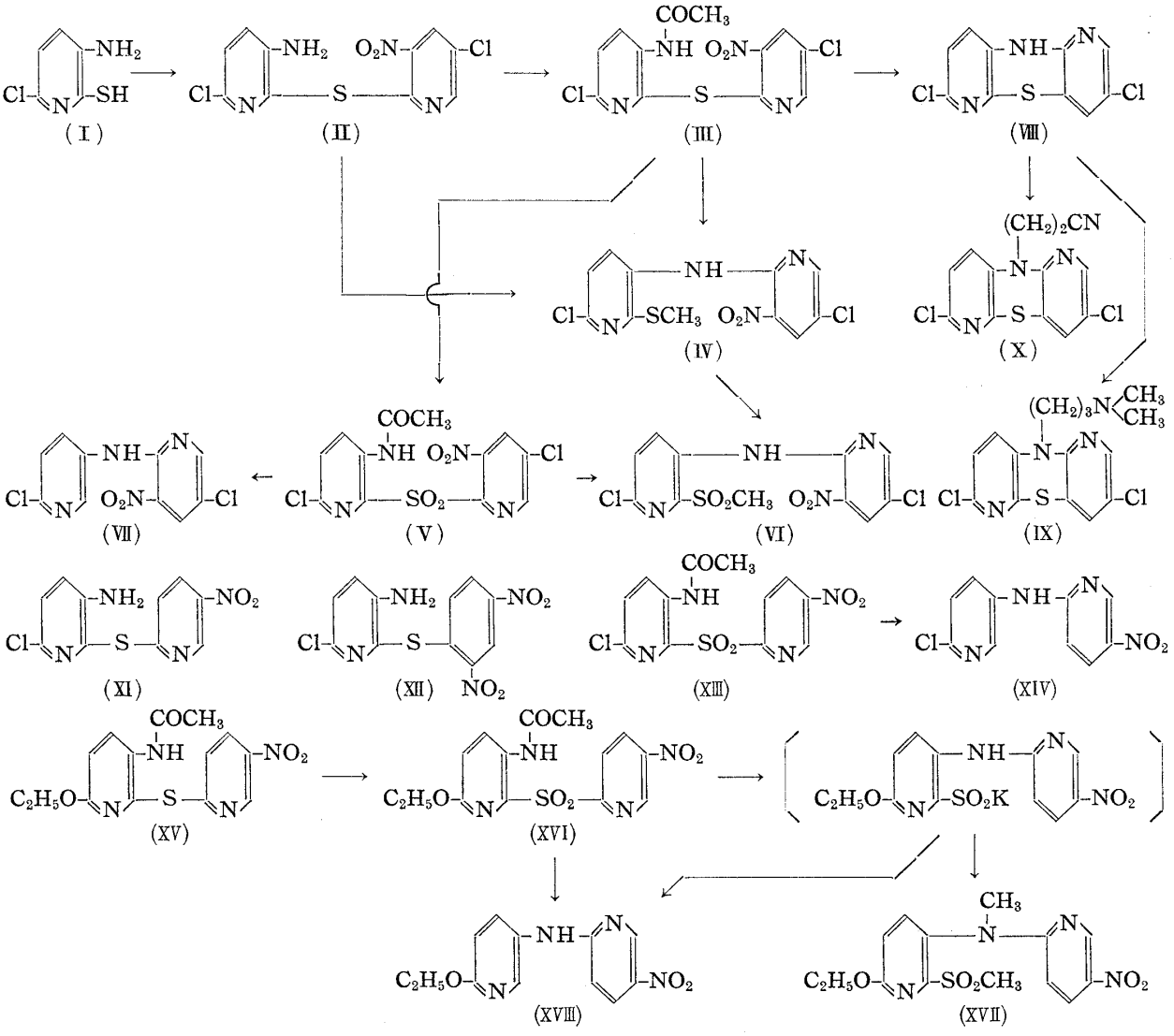


Chart 1.

* Part LV (3) : Yakugaku Zasshi, **78**, 417(1958).
** Yoshida-konoe-cho, Sakyo-ku, Kyoto (高橋酉蔵, 牧　敬文).
1) Y. Maki : Yakugaku Zasshi, **77**, 485, 862(1957).

derivatives and that the difficulty of this rearrangement depends largely upon variety of the substituent.

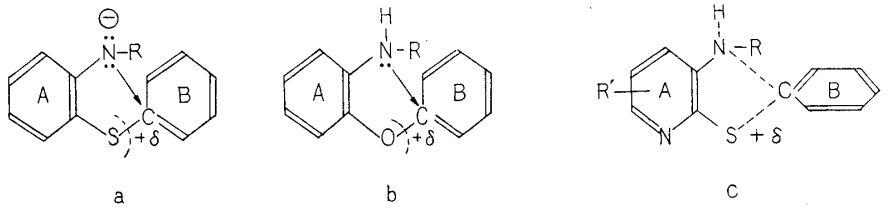
This paper describes considerations for the mechanism of the rearrangement of pyridine derivatives based on the present experimental facts and also the syntheses of N-substituted dipyridothiazine derivatives.

2-(3-Nitro-5-chloro-2-pyridylthio)-3-amino-6-chloropyridine (II), which was easily obtained from 3-amino-6-chloro-2-pyridinethiol (I),[2] and its acetate (III) underwent facile rearrangement to the methylthio derivatives (IV) in the presence of caustic alkali by the same method*,[1] as previously reported.

On the other hand, when (II) was heated in a sealed tube with methyl iodide in methanol, without the presence of caustic alkali, the expected methylamino derivative was not obtained and its rearrangement product (IV) was isolated. The same phenomenon was also observed in the case of 2-(5-nitro-2-pyridylthio)-3-amino-6-chloropyridine[1] (XI) and 2-(2,4-dinitrophenylthio)-3-amino-6-chloropyridine[1] (XII).

The above unexpected results made it necessary to investigate further, rearrangement medium other than caustic alkali. However, when heated in alcohol, pyridine, quinoline, or piperidine-alcohol mixture, no rearrangement product was isolated from either (II) or (XI).

The oxidation of 2-pyridylthio-3-acetamidopyridine derivatives to the corresponding sulfonyl derivatives (V, XIII, and XVI) was easily effected by potassium permanganate in acetic acid. For the purpose of deacetylation, the hydrolysis of these acetyl derivatives was attempted with 35% hydrochloric acid, but this brought out a truly unexpected result. For example, the rearrangement of 2-(5-nitro-2-pyridylthio)-3-acetamido-6-ethoxypyridine took place by caustic alkali at room temperature, forming sodium sulfinate from which (XVII) was derived by methyl iodide. Treatment of (XVI) with 35% hydrochloric acid, on the other hand, afforded 3-(5-nitro-2-pyridylamino)-6-ethoxypyridine (XVIII), which was identified by a mixed melting point with the compound prepared by fusion of 3-amino-6-ethoxypyridine with 2-chloro-5-nitropyridine or desulfination (Peters' method)[1,3] of the corresponding sulfinic acid.



a b c

Chart 2.

Smiles and co-workers[4] provided some factors influencing the speed of rearrangement of 2-aminophenylthio-benzene to 2-phenylamino-benzenethiol, the rearrangement of S→N type, and pointed out as one of the important factors that the amino group should be converted to anionic form before rearrangement (cf. Chart 2-a). On the contrary, Roberts and his co-worker[5] showed that the rearrangement of 2-aminodiphenyl ether to 2-hydroxydiphenylamine, the rearrangement of O→N type, differs from the usual Smiles rearrangement in not requiring conversion of the amino group to anionic form as a prerequisite to the rearrangement, i.e., the rearrangement of O→N type is initiated by the direct attack of the amino group on positive carbon atom (cf. Chart 2-b).

As indicated in the previous papers,*,[1] the rearrangement of pyridine derivatives

2) T. Takahashi, Y. Yamamoto: Yakugaku Zasshi, **71**, 196(1951).
3) W. Peters: Ber., **38**, 2567(1905).
4) S. Smiles, *et al.*: J. Chem. Soc., **1935**, 181, 340.
5) K.C. Roberts, *et al.*: *Ibid.*, **1935**, 727.

was effectively promoted by halogen atom in ring A, acyl group, and caustic alkali, which would support the above Smiles' viewpoint.

However, the above-mentioned experimental results involve some interesting problems for the interpretation of the rearrangement mechanism, as follows :

1) The presence of caustic alkali is not necessary in the rearrangement of S→N type in pyridine derivatives, and that suggests the possibility of a thermal rearrangement which includes a direct attack of amino group on positive carbon atom. Bunnet and Zahler[6] have already suggested the possibility that Smiles rearrangement might be a thermal rearrangement, and many workers have also reported examples of the cleavage of S-N. bond by direct attack of amino group.

2) From the fact that the conversion of 2-aminopyridylsulfonylpyridine into dipyridylamine is effected by hydrochloric acid, it is supposed that the rearrangement takes place even by hydrochloric acid under certain conditions. Among many literature[7] in regard to this rearrangement there is no illustration employing hydrochloric acid as a promoting agent, but an example analogous to that can be found in the Smiles report.[8] Though this reaction mechanism is not yet clear, it may be assumed that the reaction proceeds in two steps, rearrangement and desulfination, and undoubtedly, the amino group attacks positive carbon atom without the formation of an anionic form.

Subsequently, on the basis of the above findings, it should be taken into consideration that the Smiles rearrangement of S→N type of pyridine derivatives also proceeds by direct attack of the amino group, such as the above-mentioned rearrangement of O→N type.

In order to explain the rearrangement mechanism of pyridine derivatives in general, it might be most suitable to suppose a transition state as shown in Chart 2-c. Accordingly, now it should be regarded that some factors, such as halogen in ring A, acyl group (cf. Chart 2-c), and caustic alkali, have the effect of facilitating the rearrangement by advancing a loss of proton from amino group in the process through the above transition state, not in the first step before the rearrangement.

Among many phenothiazine derivatives having a basic substituent in 10-position, there are important compounds such as tranquilizing drugs in the alienism field and antihistamine drugs.

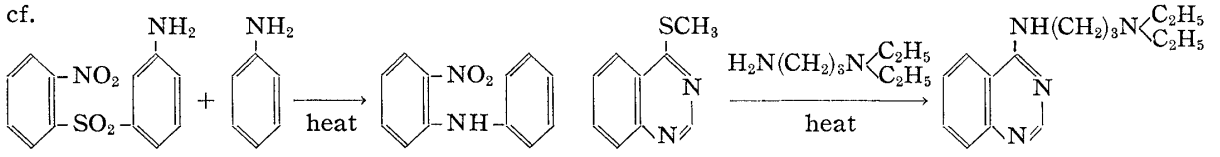
One of the purposes of the previous studies*,[1] was to obtain a compound having a more powerful activity than that of chlorpromazine from the standpoint of structural similarity with the latter, but it has not been realized either because of unstability of the ring or comparatively small amount of materials available.

However, since 3,7-dichlorodipyrido[2,3-*b*;3,2-*e*]-1,4-thiazine (Ⅷ) is an exceedingly stable and colorless material, and (Ⅷ) is obtained in comparatively good yield through

6) J.E. Bunnet, R.E. Zahler : Chem. Revs., **49**, 362(1951).

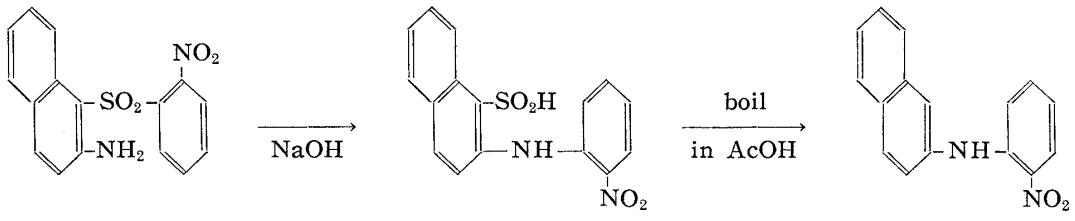
7) S. Smiles, *et al.* : J. Chem. Soc., **1932**, 1488; N.J. Leonard, *et al.* : J. Org. Chem., **11**, 349(1946).

cf.



8) S. Smiles, *et al.* : J. Chem. Soc., **1932**, 2774.

cf.



the Smiles rearrangement, (VIII) was adopted as a starting material, and was derived to 3,7-dichloro-10-(3-dimethylaminopropyl)dipyrido[2,3-*b*;3,2-*e*]-1,4-thiazine (IX) by the usual procedure.[9]

An attempt to synthesize (IX) through another route was not made because 10-cyanoethyl derivative (X) was obtained only in a poor yield by cyanoethylation using Triton B as a catalyst.

The test of pharmacological activity of (IX) was carried out by Dr. H. Fujimura of the University of Kyoto and the result will be reported in detail. Generally speaking, the toxicity of (XI) was stronger than that of chlorpromazine. Both the synergetic action with morphine and barbiturates and the effect of lowering body temperature were weaker than those of chlorpromazine.

The authors are grateful to Mr. Y. Mitsuta for his cooperation in this work and also indebted to the member of the Analytical Center of the University of Kyoto for the microanalyses.

Experimental[10]

Rearrangement of 2-(3-Nitro-5-chloro-2-pyridylthio)-3-amino-6-chloropyridine (II) and its Acetate (III)—To the solution of 2-amino-6-chloro-2-pyridinethiol (I) (4 g.) dissolved in MeOH (5 cc.) containing KOH (3 g.), 2-bromo-3-nitro-5-chloropyridine[11] (6 g.) was added with mechanical stirring for 2 hrs. at room temperature, and the solution was diluted with 4 volumes of water, giving orange-red needles (II), m.p. 205°(decomp.). Yield, 7 g. *Anal.* Calcd. for $C_{10}H_6O_2N_4Cl_2S$: C, 37.85; H, 1.89. Found: C, 37.89; H, 2.03.

Acetate (III): Light yellow needles, m.p. 188°. *Anal.* Calcd. for $C_{12}H_8O_3N_4Cl_2S$: C, 40.00; H, 2.50. Found: C, 39.83; H, 2.28.

A mixture of (II) (0.4 g.) and methanolic KOH (KOH 0.2 g., H_2O 2 cc., MeOH 10 cc.) was refluxed on a water bath until the color of the solution became red. MeI was added to the solution and the solution was allowed to stand at room temperature. The red crystals thereby obtained were recrystallized from AcOEt to red needles (IV), m.p. 189~190°. *Anal.* Calcd. for $C_{11}H_8O_2N_4Cl_2S$: C, 39.88; H, 2.42. Found: C, 39.67; H, 2.63.

(IV) was also obtained by treating (III) with methanolic KOH at room temperature, followed by addition of MeI.

A mixture of (II) or (III) (1 mole), MeI (1.2 moles), and MeOH in a sealed tube was heated in a water bath for 5 hrs. and the solution was allowed to stand at room temperature. Crystals thereby obtained were collected by filtration and identified by the mixed melting point determination with (IV) obtained as above.

(XI) and (XII) also underwent rearrangement in the same way as in the above-mentioned experiment.

In the previous paper, we reported that (XI) yielded its methylamino derivatives without rearrangement when heated in a sealed tube with MgO, MeI, and MeOH, but the structure of the product was found to be the rearrangement product after reëxamination.

3,7-Dichloro-10-(3-dimethylaminopropyl)dipyrido[2,3-*b*;3,2-*e*]-1,4-thiazine (IX)—A solution of the acetate (II) (5 g.) dissolved in a mixed solvent (acetone 20 cc., EtOH 80 cc., and H_2O 5 cc.) containing KOH (0.37 g.) was refluxed for 1.5 hrs. After removal of solvents, the residue was washed thoroughly with water, dried, and recrystallized from AcOEt to colorless needles, m.p. 250°. Yield, 4 g. *Anal.* Calcd. for $C_{10}H_5N_3Cl_2S$: C, 44.44; H, 1.85. Found: C, 44.41; H, 1.97.

A mixture of (VIII) (4 g.), $NaNH_2$ (3.0 g.), and dehyd. toluene (200 cc.) was refluxed for 6 hrs. with stirring. After cool, toluene (20 cc.) solution of dimethylaminopropyl chloride, which was obtained from 7 g. of its hydrochloride, was added, the mixture was again refluxed for 10 hrs., and concentrated *in vacuo*. The viscous residue was treated with methanolic HCl. The crystals thus obtained were collected by filtration and recrystallized from EtOH to colorless needles, m.p. 260°(decomp.). Yield, 3 g. *Anal.* Calcd. for $C_{15}H_{16}N_4Cl_2S \cdot HCl$: C, 45.98; H, 4.34. Found: C, 45.89; H, 4.59.

The hydrochloride is soluble in water and afforded a free base (IX) on treating with NaOH solution. Recrystallization from EtOH formed yellow needles, m.p. 90°. *Anal.* Calcd. for $C_{15}H_{16}N_4Cl_2S$: C, 50.70; H, 4.50. Found: C, 49.89; H, 4.86.

3,7-Dichloro-10-(2-cyanoethyl)dipyrido[2,3-*b*; 3,2-*e*]-1,4-thiazine (X)—A solution of acrylonitrile (0.2 g.) in dioxane (10 cc.) was gradually added to a mixture of (VIII) (0.5 g.), Triton B (1 cc.), and dioxane (50 cc.) with stirring, keeping the temperature between 40° and 45°. After being stirred for 3 hrs., the

9) P. Charpentier, *et al.*: Compt. rend., **235**, 59(1952); **236**, 1195(1953).
10) All melting points are uncorrected.
11) A. H. Berrie, *et al.*: J. Chem. Soc., **1952**, 2024.

solvent was removed *in vacuo*. Recrystallization of the residue from AcOEt afforded colorless needles (X), m.p. 256°. Yield, 0.15 g. *Anal.* Calcd. for $C_{13}H_8N_4Cl_2S$: C, 48.30; H, 2.48. Found : C, 48.47; H, 2.63.

Rearrangement of 2-(2-Pyridylsulfonyl)-3-acetamidopyridine Derivatives (V) to (XVI)—To a suspension of (XV) (0.3 g.) in glacial AcOH (30 cc.) an aqueous solution of $KMnO_4$ (0.23 g.) was added dropwise with stirring at room temperature. After continued stirring for 3 hrs., 30% H_2O_2 was added slowly to the reaction mixture in order to dissolve the resulting MnO_2. After diluting with 4 volumes of water, the solution was set aside at room temperature and crystals (XVI) thus obtained were collected. (XVI) was recrystallized from MeOH, yielding light yellow needles, m.p. 147~148°. Yield, 0.3 g. *Anal.* Calcd. for $C_{14}H_{14}O_6N_4S$: C, 45.90; H, 3.85. Found : C, 45.89; H, 4.00.

The oxidation of (III) to (V) was carried out by the same way as employed for (XVI), but the yield of (V) was very poor. Light yellow needles (V), m.p. 148°. *Anal.* Calcd. for $C_{12}H_8O_5N_4Cl_2S$: C, 36.87; H, 2.06. Found : C, 37.22; H, 2.38.

The mixture of (V) or (XVI) and methanolic KOH was allowed to stand at room temperature with occasional shaking. The color of the solution changed from pale yellow to red, and crystals deposited from the solution which were soluble in water and showed negative diazo reaction for primary amines. An excess of MeI was added to the solution without removing the crystals and the solution was refluxed for several minutes. After evaporation of the solvent, the residue was washed with water and recrystallized from AcOEt to orange needles (VI), m.p. 162~163°, and light yellow needles (XVII), m.p. 182~183°. *Anal.* Calcd. for $C_{11}H_8O_4N_4Cl_2S$ (VI) : C, 36.36; H, 2.29. Found : C, 36.34; H, 2.29. *Anal.* Calcd. for $C_{14}H_{16}O_5N_4S$ (XVII) : C, 47.73; H, 4.55. Found : C, 47.23; H, 4.61.

(VI) was also obtained by oxidation of (IV) with $KMnO_4$ in glacial AcOH.

Reaction of 35% HCl with 2-(2-Pyridylsulfonyl)-3-acetamidopyridine Derivatives (V, XIII, and XVI)—A solution of (XVI) in an excess of 35% HCl was heated for 2 hrs. on a water bath. After removal of HCl, the residue was recrystallized from EtOH to light yellow needles, m.p. 225°(decomp.). The analytical value of the product did not exactly agree with that of the hydrochloride of (XVIII), but it may be estimated to be the hydrochloride of (XVIII) from the fact that it is positive to Beilstein's test for halogen, absence of sulfur atom, and that it is soluble in water and converted to (XVIII) on neutralization with NH_4OH.

The identification of (XVIII) was made through admixture with the product obtained by fusion of equimolar amounts of 2-ethoxy-5-aminopyridine and 2-chloro-5-nitropyridine for 1.5 hrs.

(XVIII) was also obtained through desulfination (Peters' method) of sulfinic acid formed from (XVI) by the usual rearrangement. (XVIII) was recrystallized from EtOH-H_2O or pyridine-H_2O to form yellow needles, m.p. 180°. *Anal.* Calcd. for $C_{12}H_{12}O_3N_4$: C, 55.17; H, 4.62. Found : C, 55.08; H, 4.79.

2-(2-Pyridylsulfonyl)-3-acetamidopyridine derivatives (V and XIII) were treated with HCl in the same way as employed for (XVI) and also derived to dipyridylamines (VII and XIV),[1] which were synthesized by fusion from the corresponding pyridine derivatives.

(VII) was obtained as orange needles, m.p. 156~157°, by recrystallizing from EtOH after fusion of 2-chloro-3-aminopyridine and 2-bromo-3-nitro-5-chloropyridine. *Anal.* Calcd. for $C_{10}H_5O_2N_4Cl_2S$: C, 42.11; H, 2.11. Found : C, 42.33; H, 2.21.

Summary

1) General considerations were made concerning the mechanism of Smiles rearrangement of pyridine derivatives as a result of further investigation of reaction conditions employed.

2) A 10-substituted dipyrido-1,4-thiazine derivatives were synthesized with a view to investigating pharmacological action analogous to chlorpromazine.

(Received February 21, 1958)