Summary

Oxidation of N-(β-3′,4′-methylenedioxyphenethyl)-3-ethylpyridinium bromide by alkaline potassium ferricyanide furnished a single pyridone in a good yield. One of the writers (Tatsuno) attributed N-substituted 3-ethylpyridone-2 to this compound by measuring the dipole moment of this substance. The correctness of his deduction is now supported by an independent synthesis of the compound which was also derived from this pyridone.

(Received May 26, 1954)

45. **Torizo Takahashi, Kan-ichi Ueda, and Toshiro Ichimoto**: Sulfur-containing Pyridine Derivatives. XLI*. Synthesis of 3-Nitro-4-mercaptopyridine Derivatives and Pyrido〔3,4:4′,5′〕thiazoles.

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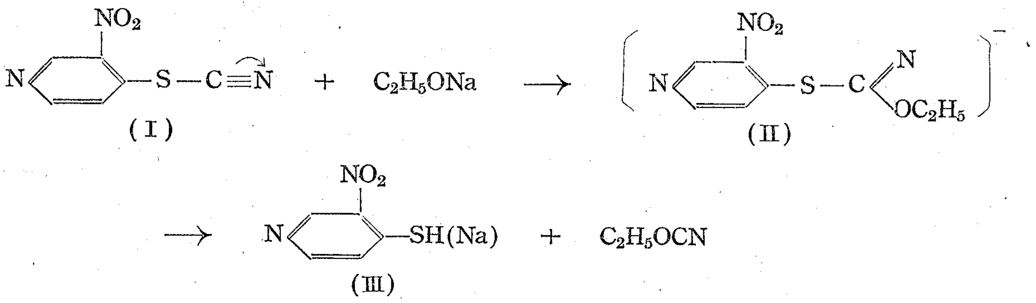
A few investigations have been made by Ross[1], and Davies and Sexton[2] about the reaction of organic thiocyano compounds with sodium ethoxide. In one of them Ross has shown that thiocyanobenzene reacted with sodium ethoxide in ethanol to give diphenyl disulfide, ethyl phenyl sulfide, and sodium thiophenate. Furthermore, in the case of 2-thiocyanobenzothiazole, Davies and Sexton reported that they obtained 2-mercaptobenzothiazole and 2-ethylthiobenzothiazole by the reaction analogous to the foregoing. In this paper, the result of the reaction of 3-nitro-4-thiocyanopyridine[3] with sodium ethoxide is described.

3-Nitro-4-thiocyanopyridine (I) was reacted with sodium ethoxide in ethanol under the same conditions as had been employed by Davies and Sexton and formed 3-nitro-4-mercaptopyridine (III)[4] in a good yield, which was ascertained by the formation of 3-nitro-4-ethylthiopyridine[4] by the reaction between (III) and C_2H_5I. In addition, formation of by-products of 3,3′-dinitrodipyridyl-(4,4′) mono- and disulfides[4] in very small amounts was observed. However, ethylthio compound corresponding to ethylthiobenzene or 2-ethylthiobenzothiazole which Ross and Davies had mentioned in their respective cases, was not obtained. This reaction mechanism can be assumed as follows:



C_2H_5OCN would isomerize to isocyanate and by combining with ethanol or sodium ethoxide, form ethyl ethylcarbamate, EtNHCOOEt, or its sodium enolate, but the latter was not detected.

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* Part XL: This Bulletin, **2**, 78 (1954).

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[1] Ross: J. Am. Chem. Soc., **56**, 727 (1934).

[2] Davies, Sexton: J. Chem. Soc., **1944**, 11.

[3] Takahashi, Ueda: This Bulletin, **2**, 34 (1954).

[4] Takahashi, Ueda: *Ibid.*, **2**, 78 (1954).

Crude (III) was then reacted with some alkyl halides; methyl and ethyl iodides, and allyl, propyl, isopropyl, and isoamyl bromides, and gave 3-nitro-4-alkylthiopyridines (IV). On reduction with stannous chloride and hydrochloric acid, (IV) yielded 3-amino-4-alkylthiopyridines (V), which on treatment with acetic anhydride was led to 3-acetamino-4-alkylthiopyridines (VI). On the other hand, potassium permanganate oxidation of (IV) in acetic acid solution yielded alkyl 3-nitropyridyl-(4) sulfones, which were reduced with stannous chloride and hydrochloric acid to the corresponding amino sulfones (VIII). (VIII) reacted with acetic anhydride to give acetamino compounds (IX). The compounds thereby obtained are listed in Tables I and II.

Finally, the preparation of pyrido[3,4:4′,5′]thiazole (X) was accomplished by the simultaneous reduction and cyclization of (III) by means of iron powder and formic acid. 2′-Methylpyrido[3,4:4′,5′]thiazole (XI) was prepared similarly, but its melting point was not sharp in spite of repeated recrystallization. Elemental analytical data, however, agreed with the values calculated from (XI). Futhermore, in order to clarify its structure, the existence of an active methyl in its molecule was examined.

(XI) reacted with benzaldehyde in the presence of anhydrous zinc chloride to yield 2′-styrylpyrido[3,4:4′,5′]thiazole (XII), and with *p*-dimethylaminobenzaldehyde, a few drops of concentrated hydrochloric acid being used as a condensing agent, to give 2′-*p*-dimethylaminostyrylpyrido[3,4:4′,5′]thiazole (XIII). The reaction route is as follows:

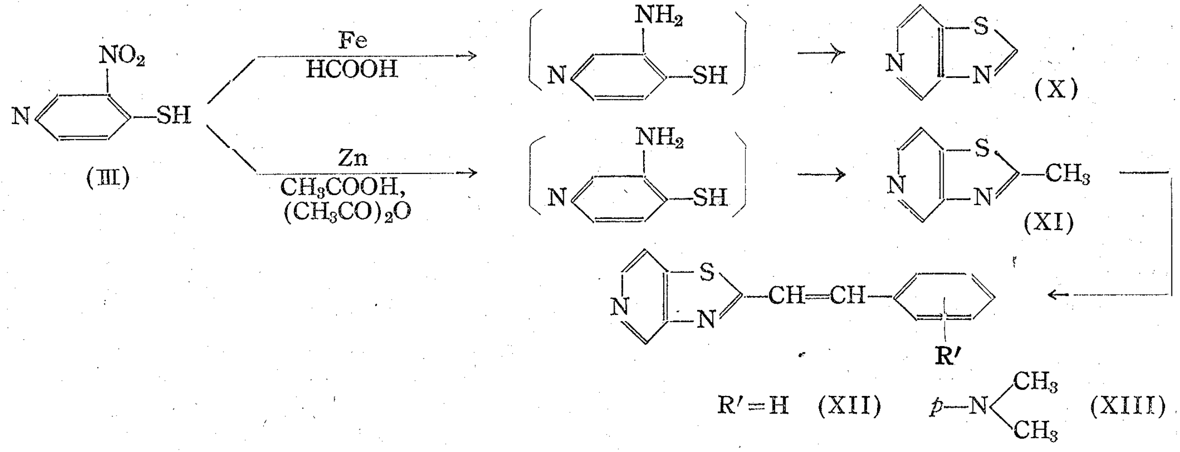
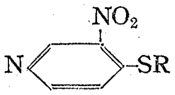


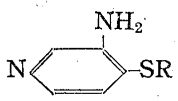
TABLE I. 3-Nitro-4-alkylthiopyridines and their Reduction Products

3-Nitro-4-alkylthiopyridines (IV)



R	m.p. (°C)	Color and crystal form	(Recrystn. solvent)	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
Methyl	133~134	Pale yellow needles	(MeOH)	$C_6H_6O_2N_2S$	42.35	42.49	3.52	3.80
Allyl	63	〃 〃	(aq. MeOH)	$C_8H_8O_2N_2S$	48.98	48.79	4.08	4.22
Propyl	75	〃 〃	(MeOH)	$C_8H_{10}O_2N_2S$	48.48	48.83	5.05	5.22
Isopropyl	64~65	〃 granules	(aq. MeOH)	$C_8H_{10}O_2N_2S$	48.48	48.32	5.05	5.30
Isoamyl	57~58	〃 crystals	(〃)	$C_{10}H_{14}O_2N_2S$	53.10	52.98	6.15	6.32

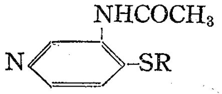
3-Amino-4-alkylthiopyridines (V)[a)]



R	m.p. (°C)	Color and crystal form	(Recrystn. solvent)	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
Methyl	165~166	Yellow needles	(MeOH)	$C_6H_8N_2S \cdot C_6H_3O_7N_3$	39.02	38.89	2.98	3.28
Ethyl	213 (decomp.)	Colorless 〃	(EtOH)	$C_7H_{10}N_2S \cdot HCl$	44.07	43.72	5.78	5.86

Allyl	211 (〃)	〃 Pillars (MeOH)	$C_8H_{10}N_2S \cdot HCl$	—	—	—	—	13.83	13.61
Propyl	191 (〃)	〃 〃 (〃)	$C_8H_{12}N_2S \cdot HCl$	46.97	47.12	6.36	6.19	—	—
Isopropyl	182 (〃)	〃 〃 (MeOH–Et$_2$O)	$C_8H_{12}N_2S \cdot HCl$	46.97	47.06	6.36	6.55	—	—
Isoamyl	182～183 (〃)	〃 crystals (Washed with Et$_2$O)	$C_{10}H_{16}N_2S \cdot HCl$	—	—	--	—	12.05	11.84

3–Acetamino–4–alkylthiopyridines (VI)



R	m.p.(°C)	Color and crystal form (Recrystn. solvent)	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
Methyl[b]	ca. 109	Colorless granules(Me$_2$CO)	$C_8H_{10}ON_2S \cdot \frac{1}{2}H_2O$	50.26	50.07	5.76	5.97	—	—
Ethyl[b]	ca. 101	〃 〃 (〃)	$C_9H_{12}ON_2S \cdot \frac{1}{2}H_2O$	52.68	52.81	6.34	6.74	13.65	13.66
Allyl[c]	151～152	Yellow needles (MeOH)	$C_{10}H_{12}ON_2S \cdot C_6H_3O_7N_3$	43.48	43.87	3.43	3.76	—	—
Propyl[c]	164	〃 plates (〃)	$C_{10}H_{14}ON_2S \cdot C_6H_3O_7N_3$	43.74	43.41	3.87	3.42	—	—
Isopropyl[b]	ca. 114	Colorless granules(Benzene)	$C_{10}H_{14}ON_2S \cdot \frac{1}{2}H_2O$	54.80	54.34	6.84	7.00	—	—
Isoamyl[c]	128～130	Yellow crystals (AcOEt)	$C_{12}H_{18}ON_2S \cdot C_6H_3O_7N_3$	46.25	46.60	4.50	4.46	—	—

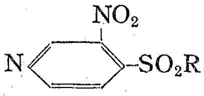
a) All the 3–amino–4–alkylthiopyridines obtained were oil and, therefore, were purified as a picrate or a hydrochloride.

b) These compounds were found by elemental analyses to be a hemihydrate.

c) These compounds were purified as a picrate by the usual method because of the difficulty of recrystallizing them due to semisolid sludge.

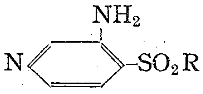
TABLE II. Alkyl 3–nitropyridyl–(4) Sulfones and their Reduction Products

Alkyl 3–Nitropyridyl–(4) Sulfones (VII)



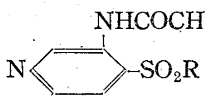
R	m.p.(°C)	Color and crystal form (Recrystn. solvent)	Formula	N, % Calcd.	N, % Found
Methyl	123	Pale yellow needles (MeOH)	$C_6H_6O_4N_2S$	13.86	14.00
Ethyl	91	Colorless needles (EtOH)	$C_7H_8O_4N_2S$	12.96	13.10
Propyl	102	〃 〃 (〃)	$C_8H_{10}O_4N_2S$	12.17	11.95

Alkyl 3–Aminopyridyl–(4) Sulfones (VIII)



R	m.p.(°C)	Color and crystal form (Recrystn. solvent)	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
Methyl	109～110	Colorless needles (Et$_2$O)	$C_6H_8O_2N_2S$	41.87	41.56	4.65	4.65	—	—
Ethyl[a]	206 (decomp.)	〃 crystals (EtOH–Et$_2$O)	$C_7H_{10}O_2N_2S \cdot HCl$	37.77	37.37	4.95	4.75	—	—
Propyl[a]	180 (〃)	〃 〃 (〃)	$C_8H_{12}O_2N_2S \cdot HCl$	—	—	—	—	11.84	11.60

Alkyl 3–Acetaminopyridyl–(4) Sulfones (IX)



R	m.p.(°C)	Color and crystal form (Recrystn. solvent)	Formula	N, % Calcd.	N, % Found
Methyl[b]	159～160	Colorless granules(AcOEt)	$C_8H_{10}O_3N_2S$	13.08	12.87
Ethyl[b]	94～95	〃 pillars (Et$_2$O)	$C_9H_{12}O_3N_2S$	12.28	12.11
Propyl	101～103	〃 granules(〃)	$C_{10}H_{14}O_3N_2S$	11.57	11.63

a) These substances were oils and were purified as the hydrochloride.

b) These products can also be prepared from 3–acetamino–4–alkylthiopyridines by oxidation with potassium permanganate.

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Experimental

Reaction of 3-Nitro-4-thiocyanopyridine (I) with Sodium Ethoxide—3-Nitro-4-thiocyanopyridine (3 g.) was added at a stretch to a stirred solution of sodium ethoxide (0.5 g. Na, in 20 cc. EtOH) maintained at 0° to 5°. The color of the solution changed to dark red. After a continued stirring for 2 hours, the solution was poured into water, and when the aqueous solution was concentated under a reduced pessure to one-third the original volume, a very small amount of a solid (20~30 mg.) separated (this was a mixture of 3,3′-dinitrodipyridyl-(4,4′) mono- and disulfides). The solid was removed by filtration and when the filtrate was neutralized with AcOH, a reddish yellow solid, decomposing at 190°, separated out. Yield, 2.3 g. This substance was comfirmed as 3-nitro-4-mercaptopyridine (III) from the fact of the formation of 3-nitro-4-ethylthiopyridine[4] on the reaction of the potassium salt of the foregoing product with ethyl iodide.

3-Nitro-4-alkylthiopyridines (IV)—To a solution of potassium hydroxide (1.2 moles) in a small amount of water were added crude (III)(1 mole), EtOH, and alkyl halide (1.2 moles), and the solution was refluxed on a water bath for 30~50 mins. The color of the solution changed gradually from dark red to reddish yellow. After being heated, the solvent was removed by distillation and several volumes of water was added. The precipitate thereby obtained was collected, washed with water, dried, and recrystallized. Yields, 60~90%.

3-Amino-4-alkylthiopyridines (V)—Addition of (IV) to a solution of an excess of stannous chloride in conc. HCl resulted in an almost clear solution with rise of temperature. The reaction mixture was heated on a boiling water bath for 30~50 mins. and then evaporated to dryness under a reduced pressure. The residue was made strongly alkaline with aq. NaOH, and extracted with ether, which was dried over anhydrous Na_2SO_4. Removal of the solvent yielded an oily product (V). The crude yields, 50~80%. Oily product was purified as the picrate or hydrochloride by the usual manner. Reduction of 3-nitro-4-allylthiopyridine was accomplished by means of iron powder and 50% of aq. AcOH in boiling EtOH for 3 hrs. Acetates (VI) : (V) was treated with Ac_2O. The reaction proceeded with a rise of temperature and when the reaction mixture was allowed to stand at a room temperature, crystals separated out. In case there was no rise of temperature and no separation of crystals occurred, the mixture was refluxed for one hour and evaporated to dryness in vacuum, after which the residue was refluxed with EtOH to decompose Ac_2O completely. After removal of EtOH, the semisolid sludge (VI) was obtained, some of which soon solidified. The semisolid sludge was purified as a picrate.

Alkyl 3-Nitropyridyl-(4) Sulfones (VII)—To a solution of (IV) in AcOH was added dropwise an aqueous solution of a calculated amount of $KMnO_4$, with stirring at room temperature. After a continued stirring for several hrs., water was added into the reaction mixture. 30% aq. H_2O_2 solution was added slowly to the reaction mixture to dissolve the resulting precipitate of MnO_2. Crystals in the reactant were collected, washed with water, dried, and recrystallized. Yields, 70~80%. However, methyl 3-nitropyridyl-(4) sulfone was obtained in a poor yield (30%).

Alkyl 3-Aminopyridyl-(4) Sulfones (VIII)—A calculated amount of stannous chloride was dissolved in conc. HCl and (VII) was added into the solution in small portions. The reduction proceeded with slight evolution of heat. The reaction mixture was heated on a boiling water bath for one hour and evaporated to dryness. A great deal of water was added into the residue, H_2S gas passed into the solution, and precipitate was filtered. The filtrate was evaporated to dryness in vacuum and the residue was neutralized with aq. potassium acetate and again evaporated to dryness. The residue was extracted with EtOAc and removal of the solvent afforded (VIII). Acetates (IX) : (VIII) was treated with Ac_2O in the same way as in the case of (VI).

Methyl(or Ethyl) 3-Acetaminopyridyl-(4) Sulfone from 3-Acetamino-4-methyl (or ethyl)-thiopyridine—After oxidation in the same way as in the case of (VII), 30% aq. H_2O_2 solution was added slowly to the reaction mixture and evaporated to dryness under a reduced pressure. The residue was extracted with ethyl acetate, after which the solvent was distilled off, leaving methyl(or ethyl) 3-acetaminopyridyl-(4) sulfone, and recrystallized. No m.p. depression was observed on admixture with those obtained above and also, corresponding aminosulfone was obtained on hydrolysis of the above-mentioned acetaminosulfone with conc. HCl.

Pyrido[3,4 : 4′,5′]thiazole (X)—A suspension of 1.5 g. of (III) in 50 g. of 80% HCOOH containing 10 g. of iron powder was boiled vigorously for 3 hours, cooled, rendered alkaline, and extracted with ether. The extract was dried over anhyd. Na_2SO_4. Removal of the solvent furnished crude (X), which was recrystallized from ether to 0.65 g. of colorless pillars, m.p. 105~106°. *Anal.* Calcd. for $C_6H_4N_2S$: C, 52.94; H, 2.94. Found : C, 52.75; H, 2.90.

2′-Methylpyrido[3,4 : 4′,5′]thiazole (XI)—To a suspension of 1.3 g. of (III) in 4 cc. of AcOH and 15 cc. of Ac_2O was added 1.5 g. of zinc dust in small portions. After vigorous reaction with rise of temperature, the content was refluxed for 3～4 hrs., cooled, and filtered. The filtrate was evaporated to dryness. The residue was rendered alkaline with aq. NaOH and extracted with ether. The ether extract was dried over anhyd. Na_2SO_4. Removal of the solvent yielded 0.65 g. of (X). Recrystallization from petroleum ether yielded colorless crystals which softened at 71° and melted at 86～89° and distilled out at 94～96°/7 mm. Hg. *Anal.* Calcd. for $C_7H_6N_2S$: C, 55.95; H, 4.07; N, 18.67. Found : C, 55.81; H, 4.30; N, 18.73.

2′-Styrylpyrido[3,4 : 4′,5′]thiazole (XII)—A mixture of 0.5 g. (XI), 1 g. of anhyd. $ZnCl_2$, and 0.6 g. of benzaldehyde in a sealed tube was heated in an oil bath (140～150°) for 8～9 hrs., after which several volumes of water was added into the content and extracted with ether. The ether extract was washed consecutively with aq. Na_2CO_3, aq. $NaHSO_3$, and water, and then dried over anhyd. Na_2SO_4. The ether was distilled off and the residue was recrystallized from alcohol to pale yellow needles (0.38 g.), m.p. 142°. *Anal.* Calcd. for $C_{14}H_{10}N_2S$: C, 70.67; H, 4.20. Found : C, 70.48; H, 4.39.

2′-*p*-Dimethylaminostyrylpyrido[3,4 : 4′,5′]thiazole (XIII)—A mixture of 0.3 g. of (XI), 0.3 g. of *p*-dimethylaminobenzaldehyde, and a few drops of conc. HCl was heated in an oil bath (100～110°) for 10 hrs. After cooling, the content was washed with aq. Na_2CO_3 and then with warm alcohol. After being dried, recrystallization from ethyl acetate yielded 0.3 g. of yellow scales, m.p. 217～218°. *Anal.* Calcd. for $C_{16}H_{15}N_3S$: N, 14.94. Found : N, 15.23.

Summary

1) 3-Nitro-4-thiocyanopyridine reacted with sodium ethoxide in ethanol to give 3-nitro-4-mercaptopyridine in a good yield, along with a small smount of 3,3′-dinitrodipyridyl-(4,4′) mono- and disulfides.

2) 3-Nitro-4-alkylthiopyridines, 3-amino-4-alkylthiopyridines, and 3-acetamino-4-alkylthiopyridines were prepared. Alkyl 3-nitropyridyl-(4) sulfones were prepared by the action of potassium permanganate on 3-nitro-4-alkylthiopyridines, and alkyl 3-aminopyridyl-(4) sulfones and alkyl 3-acetaminopyridyl-(4) sulfones were prepared.

3) The preparation of pyrido[3,4 : 4′,5′]thiazole was accomplished by the simultaneous reduction and cyclization of 3-nitro-4-mercaptopyridine and also, 2′-methylpyrido[3,4 : 4′,5′]thiazole prepared similarly. Furthermore, the condensation of benzaldehyde and *p*-dimethylaminobenzaldehyde with 2-methylpyrido[3,4 : 4′,5′]thiazole furnished 2′-styryl- and 2′-*p*-dimethyl-aminostyryl-pyrido[3,4 : 4′,5′]thiazoles.

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