21. Torizo Takahashi and Kan-ichi Ueda: Sulfur-Containing Pyridine Derivatives. XL*. Behaviour of 3-Nitro-4-thiocyanopyridine.

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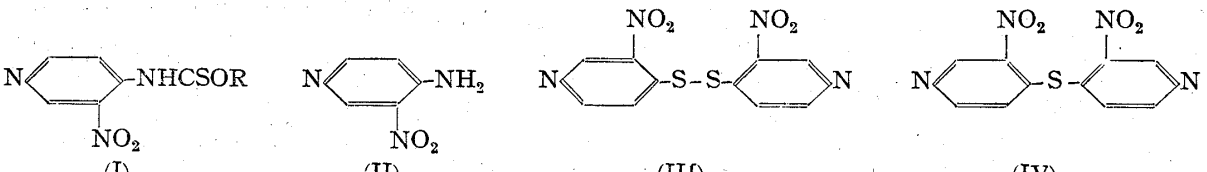
In the preceding paper[1] of this series, it was reported that when 3-nitro-4-thiocyanopyridine was heated with glacial acetic acid, 3-nitro-4-aminopyridine was produced, along with 3,3′-dinitrodipyridyl 4,4′-disulfide. This experimental fact demonstrates that the thiocyano group linked to the carbon atom at 4-position of pyridine nucleus is replaced by the amino group, and that cleavage of the linkage of the carbon atom at 4-position and the sulfur atom attached to it occurs, followed by the combination of the nitrogen atom of the thiocyano group with the carbon atom at 4-position. In this reaction, no other reagent bearing sulfur and nitrogen is provided, and it is suggested that the formation of the disulfide product occurs not from the cleavage between the bond of the carbon atom at 4-position and its neighboring atom, but from that between the S-C linkage of the thiocyano group.

Rearrangement by heat, by which thiocyano compounds isomerize to their corresponding isothiocyano compounds is known to take place among the aliphatic compounds and pyrimidine derivatives[2]. This transformation at high temperature was examined with 3-nitro-4-thiocyanopyridine. When it was heated with benzene at the refluxing temperature of benzene at ordinary pressure for 5 hrs., or at 150° or 200° under pressure for 4 hrs., no isomerization product formed by heat rearrangement was obtained, only ending in recovering the starting material. From this fact it is inconceivable that, as referred above, the transformation by which the thiocyano group of 3-nitro-4-thiocyanopyridine undergoes isomerization to the isothiocyano modification, caused an exchange of places between the sulfur atom attached to the carbon at 4-position and the nitrogen atom, and preferably it points toward some other reaction mechanism. However, it is to be considered also that under another reaction mechanism, some rearrangement similar to that mentioned above must have occurred during the course of the reaction. Studies of the reaction with glacial acetic acid furnished no information on such mechanism because it afforded only the amino product of the final stage and no intermediates.

The present paper deals with the studies on the behaviour of the foregoing thiocyano compounds towards aliphatic alcohols instead of glacial acetic acid, with considerations on the formation of the disulfide product.

(A) Reaction with Aliphatic Alcohols:

Methyl, ethyl, allyl, propyl, isopropyl, butyl, and *tert*-butyl alcohols were employed. In general, when 3-nitro-4-thiocyanopyridine was allowed to react with the foregoing alcohols, the following four kinds of products were formed:



(I) (II) (III) (IV)

R=CH_3–, C_2H_5–, *n*-C_3H_7–, *iso*-C_3H_7– and *n*-C_4H_9–.

* Part XXXIX: This Bulletin, 2, 34 (1954).

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1) This Bulletin, 2, 34 (1954).

2) Johnson, Chi: J. Am. Chem. Soc., 52, 1580 (1930); 54, 2056 (1932).

(I) is alkylthiocarbamate, the identity of which was established by the fact that an alkaline solution of the product yields precipitates on addition of acids, which, after confirmation by the analytical data, were hydrolyzed by diluted sulfuric acid to form the amino type (II). The second is 3-nitro-4-aminopyridine[3] (II), the third, 3,3'-dinitrodipyridyl 4,4'-disulfide (III), and the fourth, 3,3'-dinitrodipyridyl 4,4'-monosulfide (IV). In the case of each of the alcohols, methyl alcohol gives the above four products; ethyl, propyl, and isopropyl, and butyl alcohols, three with the exception of (II), and allyl and *tert*-butyl alcohols, three products with the exception of (I).

In this reaction it was observed that with lapse of the time of heating, color of the reaction mixture became yellow, eventually changing to yellowish-brown. In this series of experiments, however, heating was continued further for several hours to ensure the completion of the reaction. In the case of allyl and *tert*-butyl alcohols no change in the color of the reaction mixture was observed. Discussing the reaction velocity based on such change of color, the length of time required for the change of color was in the following sequence: In the case of methyl and ethyl alcohols, it took a comparatively long time; in the case of allyl alcohol, no color change was produced, and hence a suitable time was considered; with propyl alcohol, etc., a shorter time was required. Although, as a matter of course, a difference in reaction temperature exists, no appreciable influence exerted by the reaction temperature was observed, as shown in the examples of ethyl, isopropyl, and allyl alcohols. However, in the case of methyl and ethyl alcohols, a distinct difference was seen between the delay of the reaction and the yield of the disulfide and the monosulfide products, depending upon the amount used, as given in Table I.

Table I.

Material (g.)	Alcohols (cc.)	Time (hr.)	Yield of (III) (g.)	Yield of (IV) (g.)
0.8	MeOH 15	7	0.2	—
1	〃 25	12.5	0.1	0.25
1	EtOH 30	8.5	0.02	0.14
1.6	〃 45	8.5	0.03	0.3
0.8	〃 15	7	0.2	—

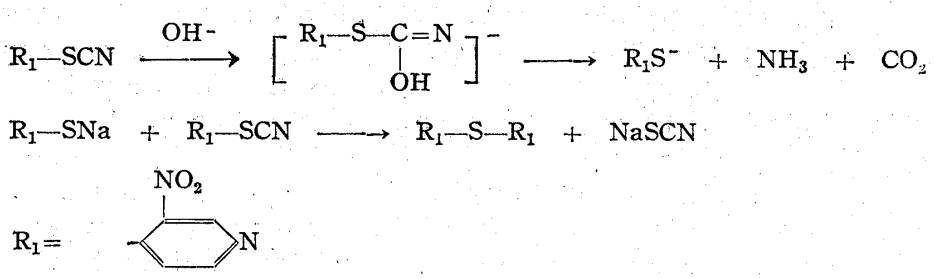
The same effect was similarly encountered in allyl alcohol but in other cases, this effect appeared to be not very remarkable. The reaction with *tert*-butyl alcohol proceeded only under pressure.

(B) Behaviour of 3-Nitro-4-thiocyanopyridine with Alkaline Solution:

3-Nitro-4-thiocyanopyridine reacted with 2*N* sodium hydroxide solution to yield 3-nitro-4-mercaptopyridine, along with small amounts of the mono- and di-sulfide products. For the identification of 3-nitro-4-mercaptopyridine, it was converted by means of ethyl iodide into 3-nitro-4-ethylthiopyridine, the identity of which was established by admixture with the corresponding product obtained by allowing 3-nitro-4-chloropyridine[4] to react with ethanethiol. 3-Nitro-4-mercaptopyridine,when recrystallized from alcohol,shows a great tendency to form an alkali-insoluble product which, from its analytical data, was confirmed to be 3,3'-dinitrodipyridyl 4,4'-disulfide. It is evident that the thiol compound readily undergoes air oxidation and changes to the disulfide type, and therefore, the crude product was used in this experiment. When the above thiol product was allowed to react with 3-nitro-4-thiocyanopyridine, slightly yellow needles, m.p. 133~134°, were obtained, which from their analytical data and the detection of the thiocyanate ion in the reaction mixture, were proved to be the monosulfide (IV). It seems clear

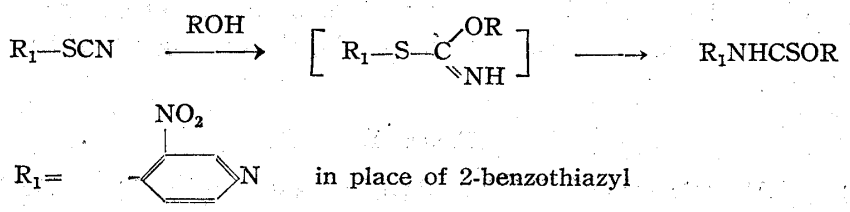
3) Koenigs, Mields, Gurlt: Ber., 57, 1183 (1924).
4) Koenigs, Fulde: Ber., 60, 2107 (1927).

that the thiocyano group of 3-nitro-4-thiocyanopyridine functions as a pseudo-halogen. Since, also in this case, the thiocyanate ion was identified in the reaction medium, the mode of change of 3-nitro-4-thiocyanopyridine in an alkaline solution may be interpreted as follows:



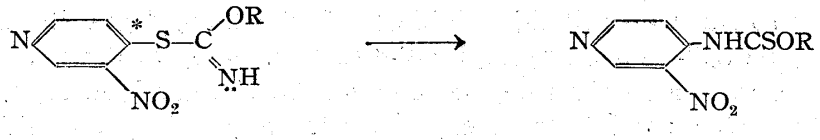
(C) Consideration of the Mechanism of the Interaction of 3-Nitro-4-thiocyanopyridine and Aliphatic Alcohols:

a) Consideration of the Mode of Formation of (I): Some time ago, Davies and Sexton[5] synthesized the benzothiazylthiocarbamate by allowing 2-thiocyanobenzothiazole to react with alcohols, and gave an explanation regarding the mechanism of their formation. If this mechanism is applied to this reaction, a similar explanation may be given as follows:



The reaction in which alcohol adds to a thiocyano group was studied by Knorr[6], and in the formation of the 2-hydroxythiazoles from thiocyanoketones, the existence of an intermediate in which a molecule of water was added to the thiocyano group was suggested earlier[7]. Therefore, in this reaction also, the formation of an intermediate addition product should be considered. If the existence of such an addition product is assumed, the formation of mono- and di-sulfide products is explainable.

As an example of the rearrangement reaction of -N=C-S- type, Davies and Sexton quoted the conversion of 2-alkylthiobenzothiazole to 2-thio-3-alkyl-2,3-dihydrobenzothiazole. In general, it is known that the diaryl sulfide possessing a nitro group at the *para*- or *ortho*-position to the sulfur atom undergoes cleavage of its sulfide group by the attack of nucleophilic reagents. The most interesting instance of this kind is provided by the Smiles rearrangement[8] which occurs with the molecule possessing an electron-donating group *ortho* to the sulfur atom.



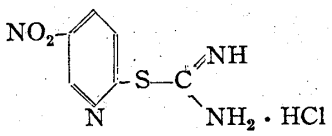
The carbon atom marked with an asterisk is active to nucleophilic reagents and the

5) Davies, Sexton: J. Chem. Soc., 1944, 11.
6) Knorr: Ber., 49, 1735 (1916).
7) Org. Reactions, VI, 377 (1951).
8) Smiles, Evans: J. Chem. Soc., 1935, 181; Wight, Smiles: *Ibid.*, 1935, 340.

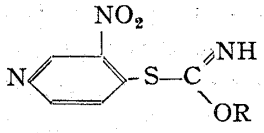
nitrogen in $-C\begin{matrix}OR\\NH\end{matrix}$ group has an electron-donating activity. Accordingly, it seems natural that the C-S linkage undergoes cleavage to cause the above rearrangement.

b) Reaction of (I) with Alcohols: Johnson and Chi[2] reported that 2-ethylthio-5-carbethoxypyrimidyl-6-thionurethane reacts with alcohol to yield 2-ethylthio-5-carbethoxy-6-aminopyrimidine. In fact, (III) was also obtained by allowing ethyl 3-nitropyridyl-4-thiocarbamate to react with ethyl alcohol under pressure. In this case, a sulfur-containing oily product was obtained, but the amount available was too small to permit further examination. It appears certain, however, that the latter is a substance possessing -CS- group, effected by cleavage of the -NH-CS- linkage. A similar reaction was experienced by heating methyl 3-nitropyridyl-4-thiocarbamate with methanol for 15 hrs.

c) Consideration of the Mode of Formation of (III) and (IV): In (a), an intermediate product with the addition of alcohol to its thiocyano group was postulated. If this intermediate is compared with that[9] obtained by allowing 5-nitro-2-chloropyridine to react with thiourea, an analogy in the structures may be seen between the two.



(V)



(VI)

(V) reacts with sodium carbonate to yield 2-mercapto-5-nitropyridine, and in an aqueous solution, it gradually decomposes and gives rise to 2-mercapto-5-nitropyridine and its monosulfide. With regard to the formation of these two products, Surrey and Lindwall[10] suggested that the intermediate must decompose to the thiol product which subsequently reacts with the original intermediate to form the monosulfide. Also, they demonstrated that 5-nitro-2-chloropyridine reacts with 5-nitro-2-thiopyridine to afford the monosulfide.

By analogy with (V), the mercapto product may be produced first from the intermediate (VI). Subsequent formation of the monosulfide (IV) may be brought about by reaction between the resulting thiol product and the thiocyano compound, considering the detection of thiocyanate ion and the volume effect experienced with methyl and ethyl alcohols. On the other hand, the disulfide may be formed by the mercapto product not participating in the reaction with the thiocyano compound, undergoing air oxidation. Many papers[11] have appeared regarding the reaction between the active chloro compounds and thiourea. Watt studied the reaction between 2-chlorobenzothiazole and thiourea and pointed out that the proportion of the formation of the thiol and monosulfide products depends on the stability of the intermediate or the ion produced therefrom. Mention was made earlier that 3-nitro-4-mercaptopyridine reacts with 3-nitro-4-thiocyanopyridine to furnish the monosulfide (IV). It is considered that this reaction has some relation to the volume effect of alcohols, already referred to, but the experimental results revealed that in effect, it was not affected whatever by the volume of solvents employed. If the volume effect is assumed to be based upon the function of the intermediate, it can be explained in a satisfactory manner as follows:

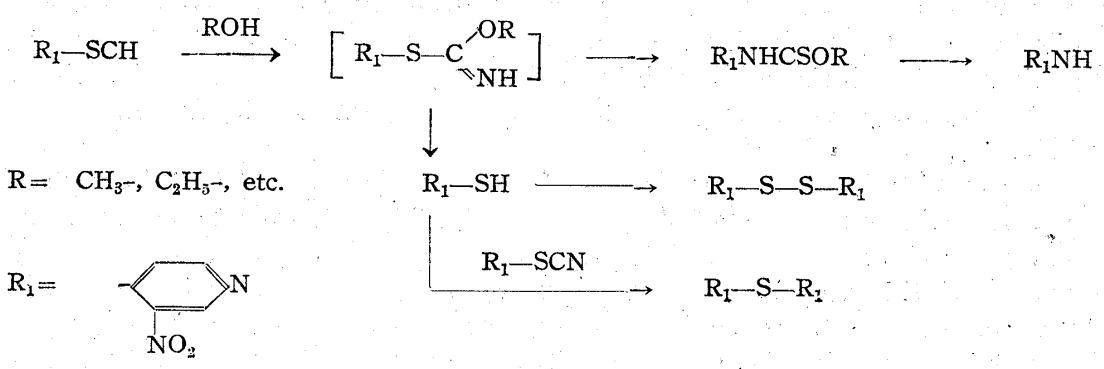
9) 10) Surrey, Lindwall: J. Am. Chem. Soc., 62, 1697 (1940); Phillips, Shapiro: J. Chem. Soc., 1942, 584.

11) Watt, Scott: J. Org. Chem., 2, 148 (1939); Watt: *Ibid.*, 4, 436 (1939); Rosenhauer: Ber., 62, 2730 (1929).

$$R_1\text{—SCN} + ROH \rightleftarrows \left[R_1\text{—S—C}\begin{matrix}\diagup OR \\ \diagdown NH\end{matrix} \right] \rightleftarrows \left[R_1\text{—S—C}\begin{matrix}\diagup OR \\ \diagdown N\end{matrix} \right]^- + H^+$$

As Watt pointed out, the stability of the intermediate and its ion may change according to the variety of R, but if in the case of methyl and ethyl alcohols, the intermediate is assumed to be stable to some extent, the delay of the reaction by their volume must be accounted for by the fact that the above equation is largely progressing to the left, being influenced by H^+ produced from alcohol. While the intermediate gradually decomposes to the thiol product, the unreacted R_1SCN and R_1SH react with each other, and subsequently, the formation of the monosulfide (IV) becomes remarkable. It seems natural, therefore, that with alcohols, especially with methyl and ethyl alcohols, its effect becomes great, but in this cases, the problem arising from the activity of solvents may be taken into account.

The above considerations and experimental results lead to the following conclusion. In the first place, alcohols add to 3-nitro-4-thiocyanopyridine and an intermediate addition product is formed. Subsequently, the linkage between the carbon at 4-position of the pyridine nucleus in this intermediate and sulfur undergoes cleavage to result in a rearrangement reaction. This is followed by the cleavage of the S–C linkage of the thiocyano group to yield the mercapto product, which in turn reacts with the thiocyano group of 3-nitro-4-thiocyanopyridine functioning as pseudo-halogen, and affords the monosulfide product. The formation of the amino type and disulfide effected by the action of alcohols and air oxidation, is understood to be a secondary reaction. The reason why (I) is not obtained in the case of allyl and *tert*-bytyl alcohol, may be attributed to the instability of (I), which rapidly changes to the amino type. The relationship among these is shown in the accompanying diagram.



In the reaction with glacial acetic acid, a similar consideration based on that with alcohols is made. The fact that in this case similar products are furnished as in the case of allyl and *tert*-butyl alcohols indicates that under the mechanism analogous to that shown in the cases of alcohols, the amino and disulfide products may be formed. In this case, no monosulfide product could be obtained, the volumes of glacial acetic acid employed making no difference. This is probably because glacial acetic acid has a greater activity than alcohols, and though no monosulfide product could be obtained because of its very small amount, it was formed, since in the reaction mixture, trace of SCN^- was detected.

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Experimental

3-Nitro-4-ethylthiopyridine—To a solution of 1.2 g. of potassium hydroxide in 5 cc. of water was added 0.7 g. of ethanethiol. The above solution was combined with a solution of 2 g. of 3-

nitro-4-chloropyridine hydrochloride in 5 cc. of dioxane, and the mixture stirred. A vigorous reaction took place with evolution of heat. After stirring for several hours, water was added to the reaction mixture, and the deposited crystals were filtered, washed with water, and dried. They were recrystallized from methanol to form slightly yellow needles, m.p. 86°. Yield, almost quantitative. *Anal.* Calcd. for $C_7H_8O_2N_2S$: C, 45.65; H, 4.33. Found: C, 45.96; H, 4.73

3-Nitro-4-mercaptopyridine—0.7 g. of 3-nitro-4-thiocyanopyridine was warmed with 3 cc. of 2*N* NaOH on a water bath at 60° for 2 hrs. The color of the reaction mixture changed to dark red with evolution of ammonia. After the completion of the reaction, the reaction mixture was filtered once to remove alkali-insoluble materials, and the filtrate neutralized by the addition of acetic acid, depositing 0.56 g. of the crude red crystals, m.p. 190° (decomp.). When this product was repeatedly recrystallized from alcohol, it changed to an alkali-insoluble meterial, which after recrystallization from dioxane, crystallized in the form of yellow granules, m.p. 233° (decomp.), identical with 3,3′-dinitrodipyridyl 4,4′-disulfide. *Anal.* Calcd. for $C_{10}H_6O_4N_4S_2$: N, 18.06. Found: N, 18.01.

The potassium salt of the crude mercapto compound, when allowed to react with ethyl iodide, furnished the above 3-nitro-4-ethylthiopyridine. Meanwhile, the alkali-insoluble materials removed by filtration of the reaction mixture were separated into two kinds by treating with methanol. One was 3,3′-dinitrodipyridyl 4,4′-disulfide (yield, 20 mg.) and the other, 3,3′-dinitrodipyridyl 4,4′-monosulfide (yield, 40 mg.), the identity of which was confirmed by admixture of the monosulfide, m.p. 133~134°, prepared from the mercapto and the thiocyano compounds.

3,3′-Dinitrodipyridyl 4-4′-Sulfide—40 mg. of 3-nitro-4-mercaptopyridine was mixed with 46 mg. of 3-nitro-4-thiocyanopyridine, and 2 cc. of ethanol was added to the mixture. On gently warming on a water bath, a reaction immediately occured. Thiocyanate ion was identified in the reaction medium. After the reaction had subsided, the solid material pricipitated on adding aq. Na_2CO_3 was collected by filtration, washed with water, and dried. Recrystallization was effected from methanol to slightly yellow needles, m.p. 133~134. Yield, 90%. *Anal.* Calcd. for $C_{10}H_6O_4N_4S$: C, 43.20; H, 2.15; N. 20.14; S, 11.53. Found: C, 43.03; H, 2.05; N, 19.94; S, 11.87. This product was also obtained by using 0.5 cc. of ethanol or by allowing to stand for 2 days.

Reaction with Alcohols—With Methanol: a) A mixture of 0.8 g. of 3-nitro-4-thiocyanopyridine and 15 cc. of methanol was refluxed on a water bath. The color of the reaction mixture gradually became yellow, which after the lapse of 6 hrs., changed to yellowish brown. Heating was continued for further 1 hr. After cooling, the deposited yellow crystals were filtered and recrystallized from dioxane, yielding 0.2 g. of yellow granules, m.p. 233° (decomp.), identical with the disulfide (III). Meanwhile, the filtrate was freed of the solvent and the residue treated with 10% NaOH. The insoluble material which precipitated out was collected by filtration, washed with water, and dried. By recrystallization from ethyl acetate, it crystallized in the form of slightly yellow needles, m.p. 200°, undepressed by admixture with 3-nitro-4-aminopyridine (II). Yield, 0.12 g. On the other hand, the alkaline filtrate was neutralized by acetic acid, and deposited a solid material, which was filtered, and dried. Recrystallization from ether-petroleum ether yielded 0.25 g. of slightly yellow needles, m.p. 97~98°. This substance was methyl 3-nitropyridyl-4-thiocarbamate. *Anal.* Calcd. for $C_7H_7O_3N_3S$: C, 39.44; H, 3.29; N, 19.72. Found: C, 39.79; H, 3.24; N. 19.70. The neutralized filtrate, after being allowed to stand, afforded further minute amount of (III).

b) One g. of 3-nitro-4-thiocyanopyridine was heated with 25 cc. of methanol on a water bath. After the lapse of 12 hrs., the reaction mixture became yellow brown. Heating was continued for further 30 minutes, and then the whole was concentrated to one-half its volume. When allowed to cool by standing, crystals appeared, which were collected by filtration and recrystallized from methanol to form slightly yellow needles, m.p. 133~134°, undepressed by admixture with a sample of (IV); yield, 0.23 g. The filtrate, after complete evaporation of the solvent, was treated in the same manner as in the case of (a); 0.32 g. of methyl 3-nitropyridyl-4-thiocarbamate, 50 mg. of the amino form (II), and 0.1 g. of the disulfide form (III) were obtained.

With Ethanol: a) One g. of 3-nitro-4-thiocyanopyridine was heated with 30 cc. of ethanol under reflux on a water bath. After the lapse of 8 hrs., the content became yellowish brown, and heating was continued for a further 30 minutes. After cooling, the deposited crystals were treated with warm methanol, and separated into the disulfide (III) (20 mg.) and the monosulfide (IV). The filtrate was freed of alcohol and the residue was treated with 10% NaOH to separate into the alkali-soluble and -insoluble portions. The alkali-insoluble portion consisted of 0.14 g. of the monosulfide (IV). The alkali-soluble portion was neutralized by acetic acid, and the crystals which resulted were collected, washed with water, and dried. Recrystallization from a mixture of ether and petroleum ether gave yellow needles, m.p. 67~68°; yield, 0.48 g. To this product was added water and a few drops of conc. H_2SO_4 and the mixture was heated over flame for 2.5 hrs. The reaction mixture was then allowed to cool and after neutralization with aqueous ammonia, extracted with ethyl acetate, yielding the amino compound. On the basis of this reaction and analytical data, the ethanol reaction

product was identified as ethyl 3-nitropyridyl-4-thiocarbamate. *Anal.* Calcd. for $C_8H_9O_3N_3S$: C, 42.29; H, 3.95; N, 18.50. Found: C, 41.99; H, 3.94; N, 18.20.

b) The preparation was effected by using 1.6 g. of 3-nitro-4-thiocyanopyridine and 45 cc. of ethanol, following the same procedure as employed in (a); 30 mg. of the disulfide (III), 300 mg. of the monosulfide (IV), and 900 mg. of ethyl 3-nitropyridyl-4-thiocarbamate were obtained.

c) A solution of 0.8 g. of the thiocyano compound in 15 cc. of ethanol was refluxed on a water bath for about 6 hrs., when a reddish brown color developed. After heating for an additional hour, the solution was cooled by standing and deposited 0.12 g. of the disulfide. The filtrate from these crystals was freed of alcohol, the residue was treated with 10% NaOH, and neutralized with acetic acid, depositing 0.45 g. of ethyl 3-nitropyridyl-4-thiocarbamate. The filtrate, after standing, furnished a further crop of the disulfide (III), weighing 0.08 g.

With Propyl Alcohol: 0.8 g. of the thiocyano compound was heated with 10 cc. of propyl alcohol on a water bath. Heating was continued for 1.5 hrs. by which a yellowish brown color resulted, and the reaction was completed by heating further for 40 minutes. After cooling, the depositing crystals were filtered with suction and treated with methanol to separate into 0.32 g. of the disulfide and 30 mg. of the monosulfide. The filtrate was freed of alcohol and to the residue was added 10% NaOH. In this case 30 mg. of the monosulfide was obtained as an alkali-insoluble material. The alkaline solution was neutralized by acetic acid, and deposited an oily product, which was taken up in ether. The ether extract was dried over anhydrous Na_2SO_4. On removal of the ether, an oily material remained, which on addition of a few drops of conc. HCl crystallized out. It was filtered, dried, and recrystallized from a mixture of alcohol and ether to form a slightly yellow needles, decomposing at 152° and weighing 0.5 g. This product was propyl 3-nitropyridyl-4-thiocarbamate hydrochloride. *Anal.* Calcd. for $C_9H_{11}O_3N_3S \cdot HCl$: C, 38.92; H, 4.32; N, 15.14. Found: C, 39.01; H, 4.56; N, 15.03. The solution left after extraction with ether yielded an additional 10 mg. of the disulfide (III).

With Isopropyl Alcohol: 0.7 g. of 3-nitro-4-thiocyanopyridine was refluxed with 10 cc. of isopropyl alcohol on a water bath. After a lapse of 2.5 hrs., the reaction mixture became brown, after which time heating was continued for a further 30 minutes. Treatment by the same procedure as in the case of propyl alcohol gave isopropyl 3-nitropyridyl-4-thiocarbamate hydrochlride, m.p. 176° (decomp.). Recrystallization was effected from a mixture of ether and alcohol to slightly yellow needles; yield, 0.4 g. *Anal.* Calcd. for $C_9H_{11}O_3N_3S \cdot HCl$: N, 15.14. Found: N, 15.22. 40 mg. of the disulfide and 0.18 g. of the monosulfide were obtained in a similar manner.

With Butyl Alcohol: The preparation was carried out by heating 1 g. of 3-nitro-4-thiocyanopyridine with 12 cc. of butyl alcohol on a water bath for 2 hrs. The products were treated as above. Along with 0.98 g. of the disulfide (III) and 70 mg. of the monosulfide (IV), 0.5 g. of butyl 3-nitropyridyl-4-thiocarbamate, forming yellow crystals, m.p. 148° (decomp.), was obtained. *Anal.* Calcd. for $C_{10}H_{13}O_3N_3S \cdot HCl$: N, 14.41. Found: N, 14.33. This hydrochloride was hydrolyzed by dil. H_2SO_4 to the amino compound (II).

With Allyl Alcohol: a) One g. of the thiocyano compound was heated with 12 cc. of allyl alcohol on a water bath, at the end of which time the reaction mixture became only slightly yellow. After cooling, the solvent was removed, and 10% NaOH solution was added to the remaining muddy residue, yielding yellow crystals. They were recrystallized from ethyl acetate and melted at 200°. This product was the amino compound (II). Yield, 0.5 g. Neutralization of the alkaline filtrate by acetic acid gave no product, but on standing, 0.11 g. of the disulfide (III) appeared. b) 0.6 g. of the thiocyano compound was heated with 12 cc. of allyl alcohl for 4 hrs. In this case, approximately 40% of the starting material was recovered. After removal of the solvent, the residue was treated with cooled methanol to separate into two portions. The portion insoluble in cold methanol was recrystallized from methanol, m.p. 130~134°. The identity of this product with the monosulfide (IV) was established by the mixed melting point determination. The methanol-soluble portion afforded a small amount of the amino compound.

With *tert*-Butyl Alcohol: A mixture of 0.8 g. of the thiocyano compound and 10 cc. of *tert*-butyl alchol was heated in a sealed tube at 140~150° in an oil bath for 6 hrs. The reaction mixture was allowed to cool, and gave 0.2 g. of yellow crystals, which corresponded to the disulfide (III). The filtrate left after separation from the disulfide furnished about 0.5 g. of the amino type (II). Heating at ordinary pressure for 7 hrs. only ended in recovering the starting material.

Reaction of Thiocarbamates with Aclohols—With Ethanol: 0.4 g. of ethyl thiocarbamate was heated with 15 cc. of ethanol between 120° and 130° in an oil bath for 7 hrs. After completion of the reaction, the alcohol was removed, the residue was dissolved in 10% NaOH solution, and extracted with ethyl acetate. After drying over anhydrous Na_2SO_4, the solvent was removed, leaving a muddy residue. This was washed with ether and recrystallized from ethyl acetate; m.p. 200°, yield, 0.1 g. This product corresponded to the amino type (II). The ether washings were concentrated and left a sulfur-containing oil.

With Methanol: 0.3 g. of methyl thiocarbamate was refluxed with 6 cc. of methanol on a water bath for 19 hrs. After the reaction was complete, the reaction mixture was treated with 10% NaOH solution and extracted with ethyl acetate. After removal of the solvent, the residue was washed with ether and yielded 60 mg. of the amino compound, m.p. 200°.

Summary

In general, when 3-nitro-4-thiocyanopyridine is allowed to react with aliphatic alcohols, four kinds of products are formed, namely, the alkyl thiocarbamates, 3-nitro-4-aminopyridine, 3,3′-dinitrodipyridyl 4,4′-disulfide, and 3,3′-dinitrodipyridyl 4,4′-monosulfide, and this reaction mechanism was considerated.

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22. Shigehiko Sugasawa and Koji Oka: Synthesis in the Benzoquinolizine Group. XXIII.[1] Synthesis of *rac*-C-bisnoremetine.

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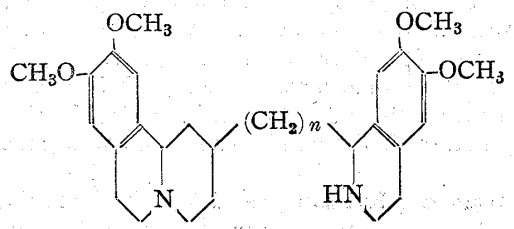
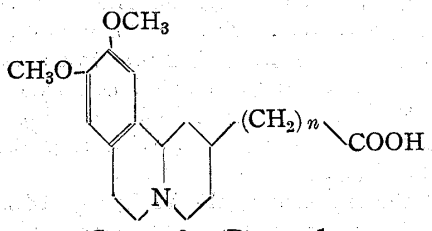
The preceding paper[1] of this series described a synthesis of *rac*-C-trisnoremetine (A). The compound (C), which formed one of the intermediates in the above synthesis, appeared to be also a suitable material for the synthesis of *rac*-C-bisnoremetine (B) in case the corresponding homoacid (D) is obtainable from (C) by Arndt-Eistert method. Our efforts to this end, however, ended fruitless because of the difficulty of preparing the chloride of the acid (C) pure enough, so that the Arndt-Eistert reaction can be carried out satisfactorily. This difficulty is probably due to the amphoteric character of the acid (C).



(A): n=0; (B): n=1



(C): n=0; (D): n=1

So we next turned our attention to N-β-3′,4′-dimethoxyphenethylpyrid-2-one-4-carboxylic acid (I), the precursor of (C), whose chloride is expected to be obtainable in higher state of purity because of the nonbasic character of the nitrogen present in the molecule. However, the preparation of the chloride first met with some difficulty, which was, however, overcome by using an excess of oxalyl chloride as the chlorination agent in the presence of a small amount of pure pyridine at an ordinary temperature. The crude diazoketone, which was prepared by the usual method from this acid, was directly treated with β-3,4-dimethoxyphenethylamine in the presence of silver nitrate, giving the amide (III), which was then reduced catalytically to yield the corresponding piperidone derivative (IV) as colorless needles of m.p. 130~131°.

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1) This Bulletin, 1, 230 (1953).