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Torizo Takahashi and Kan-ichi Ueda : Sulfur-containing Pyridine Derivatives. XLVII.* Behavior of 3-Nitro-4-thiocyanopyridine to Aliphatic Alcohols. (2).

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

In Part XL[1] of this series, the authors reported of an interesting behavior of the thiocyano group in 3-nitro-4-thiocyanopyridine (I) toward aliphatic alcohols, and it was suggested that the main product in this reaction should be the alkyl thiocarbamate (II) from the fact that it was soluble in alkali, recoverable unchanged on addition of acids, and on hydrolysis it formed the aminopyridine (IV).

In order to define the structure of the above product more clearly, it was submitted to oxidation (Kitamura's reaction[2]), which led to the urethane. The latter was confirmed by synthesizing it from the aminopyridine and by direct comparison of their infrared spectra, the details of which follow.

Treatment of ethyl 3-nitropyridyl-4-thiocarbamate (II) with hydrogen peroxide in aqueous potassium hydroxide solution provided the sulfurless product of m.p. 63°, which was found to be identical with the product (III) obtained by the condensation of 3-nitro-4-aminopyridine[3] (IV) and ethyl chlorocarbonate. The infrared absorption spectrum of (III) (Fig. 1) shows a characteristic absorption for NH type near 3 μ in addition to the carbonyl absorption (5.74 μ), but that of (II) (Fig. 2) does not show the carbonyl absorption, although absorption by NH type is present. This indicates that

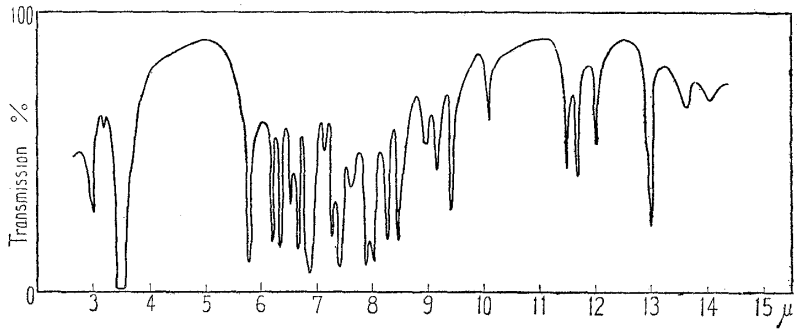

Fig. 1. 3-Nitropyridyl-4-carbamate (in Nujol)

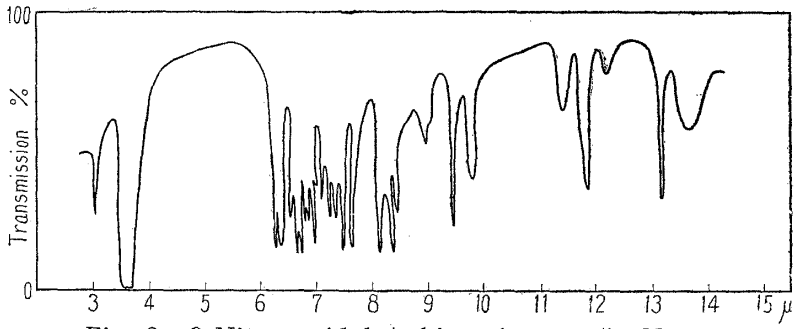

Fig. 2. 3-Nitropyridyl-4-thiocarbamate (in Nujol)

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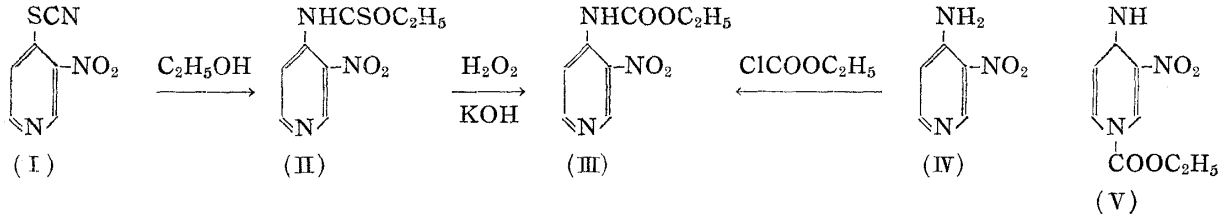
** Yoshida-konoe-cho, Sakyo-ku, Kyoto (高橋酉蔵, 上田寛一).

1) T. Takahashi, K. Ueda : This Bulletin, **2**, 78(1954).
2) R. Kitamura : J. Pharm. Soc. Japan, **58**, 29(1938).
3) E. Koenigs, M. Mields, H. Gurlt : Ber., **57**, 1183(1924); T. Takahashi, K. Ueda : This Bulletin, **2**, 34(1954).

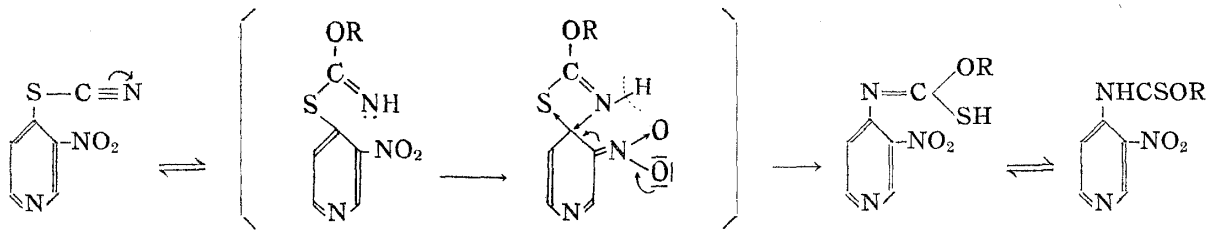
>C=S group of the alkyl thiocarbamate (II) was converted to the carbonyl group.

Long time ago, Camps[4] reported the synthesis of pyridyl-4-urethane from γ-aminopyridine and ethyl chlorocarbonate. However, when α- or γ-aminopyridine is allowed to react with a compound containing active chlorine atom, two possible structures may well be considered for the product formed (cf. reaction of α-aminopyridine with monochloroacetic acid). Although in this case the structure of pyridonimide type (V) may similarly be considered, it is evident that it is not of pyridonimide type but of aminopyridine type (III), since it was shown to be identical with the product formed from (II). Similarly, methyl 3-nitropyridyl-4-urethane (VI) was prepared by the oxidation of methyl thiocarbamate with hydrogen peroxide.



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

Accordingly, as shown in an earlier paper,[1] the mechanism of the formation of alkyl thiocarbamates in the reaction of (I) with alcohols may be interpreted as follows: Alcohols first add to (I) to form an intermediate addition product, which subsequently undergoes rearrangement accompanied by an intramolecular nucleophilic substitution.



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

Moreover, it had been shown that in the case of methanol and ethanol, a distinct difference was seen in the delay of the reaction and the yield of the disulfide and the monosulfide product, depending upon the amount used. However, in the case of dehydrated alcohols, the further delay of the reaction was brought about, which suggested ionic reaction mechanism, especially when a large amount of dehydrated alcohols was employed, greater part of the starting materials being recovered even after refluxing for 14 hours.

The volume effect of alcohols, already referred to, was assumed to be based upon the function of the intermediate addition product and ion, but it seems unnatural to consider the existence of the ionic form from the fact that the compound containing an imidoether group is generally a strong base. This matter will be discussed after a more detailed studies on the kinetics have been made. According to the experimental results, however, the more the reaction delays, the more striking the formation of the monosulfide becomes, and hence the formation of the monosulfide appears to be decided by the rate of the first addition reaction.

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4) R. Camps: Arch. Pharm., **240**, 345(1902).
5) A. E. Tschitschibabin: Ber., **57**, 2092(1924); F. Reidel, H. Rauch: *Ibid.*, **58**, 393(1925).

Experimental[6]

Reaction with Ethanol—a) The preparation was effected by using 1.0 g. of 3-nitro-4-thiocyanopyridine and 30 cc. EtOH, following the same procedure as described in the experimental section of Part XL, and in this case 30 mg. of 3-nitro-4-aminopyridine, which was not described previously, was obtained besides other products. The m.p. of ethyl 3-nitropyridyl-4-thiocarbamate registered 74° after repeated recrystallization from petr. ether-ether. *Anal.* Calcd. for $C_8H_9O_3N_3S$: N, 18.50. Found: N, 18.68.

b) 1.0 g. of the thiocyano compound was heated with 25 cc. of dehyd. EtOH for 14 hrs. In this case, approximately 75% of the starting material was recovered.

Methyl 3-Nitropyridyl-4-carbamate—To a solution of 0.4 g. of methyl 3-nitropyridyl-4-thiocarbamate in aq. KOH solution (0.4 g. of KOH, 8 cc. of water) was added dropwise 4 cc. of 30% H_2O_2 under cooling, and after being allowed to stand at room temerature for 1 hr., the mixture was adjusted to pH 7. The product thus obtained was collected, washed with water, dried, and recrystallized from MeOH to colorless pillars, m.p. 140~142°. Yield, 0.33 g. *Anal.* Calcd. for $C_7H_7O_4N_3$: C, 42.64; H, 3.55. Found: C, 42.61; H, 3.82.

Ethyl 3-Nitropyriyl-4-carbamate—a) In a flask fitted with a mechanical stirrer were placed 0.4 g. of 3-nitro-4-aminopyridine, 0.16 g. of Na_2CO_3, 20 cc. of ether, and 2 cc. of water. To the two-phase system was added dropwise with stirring 0.60 g. of $ClCOOC_2H_5$ during 30 mins. After the addition had been completed, stirring was continued for a further 30 mins. At the end of this period, the organic layer was separated. The aqueous layer was extracted with ether and these ethereal extracts were combined with the initial organic phase. After washing with water and drying over anhyd. Na_2SO_4, the ether was distilled off and the residue was recrystallized from petr. ether to colorless needles, m.p. 62°. Yield, 0.16 g. *Anal.* Calcd. for $C_8H_9O_4N_3$: N, 19.91. Found: N, 19.82.

b) To a solution of 0.5 g. of the thiourethane in aq. KOH (0.5 g. of KOH, 8 cc. of water) was added dropwise 3.0 cc. of H_2O_2 under cooling, and the mixture was treated by the same procedure as described for the preparation of the methyl carbamate. Yield, 0.31 g. After recrystallization from petr. ether, this product showed no m.p. depression on admixture with the above-mentioned sample.

Summary

1) The application of Kitamura's reaction to ethyl 3-nitropyridyl-4-thiocarbamate resulted in the formation of ethyl 3-nitropyridyl-4-carbamate, which was identical with the product obtained by the reaction of 3-nitro-4-aminopyridine with $ClCO_2C_2H_5$.

2) The reaction mechanism of the thiocyano compound with alcohols was reconsidered.

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6) All melting points are uncorrected.