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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XVII.[1] Reaction of 1-Methyl-2(1*H*)-thiopyridone with Hydrochloric Acid and Formaldehyde

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Reaction of 1-methyl-2(1*H*)-thiopyridone with formaldehyde and hydrochloric acid was carried out. The main product in this reaction was 3-hydroxymethyl-1-methyl-2(1*H*)-thiopyridone (IV) in 22% yield. The structure of products in this reaction were confirmed by their nuclear magnetic resonance spectral comparison.

1-Methyl-2(1*H*)-pyridone (I) can easily be synthesized from pyridine in two steps and can be reverted to pyridine. Electrophilic substitution reaction of I, such as the Mannich reaction[3] and the reaction with formaldehyde and hydrochloric acid,[4] takes place at 5-position, which are different from those in pyridine N-oxide. Therefore, I is rather interesting as the intermediate for the synthesis of pyridine derivatives. 1-Methyl-2(1*H*)-thiopyridone[5] (II), easily obtained in one step from I, is likely to have 3- and 5-positions react to electrophilic substitution similar to I, considering its resonance canonical formulae. Unexpectedly, however, reaction of II with methyl iodide gives the S-methylated compound[6] (III) while a similar O-methylated compound is never formed by the same treatment of I, as shown in Chart 1. It is usual to assume that oxygen compounds and sulfur compounds behave similarly but I and II apparently differ in their behavior. Since there is no report on the substitution reactions of II, we attempted various reactions of II and its derivatives. The present paper deals with the reaction of II with formaldehyde and hydrochloric acid. Before carrying out the reaction on II, nuclear magnetic resonance (NMR) spectral assignment of II was

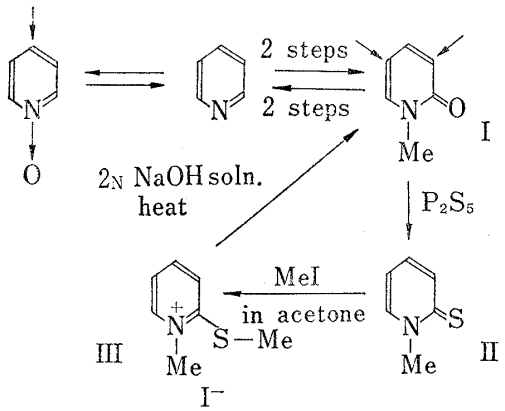

Chart 1

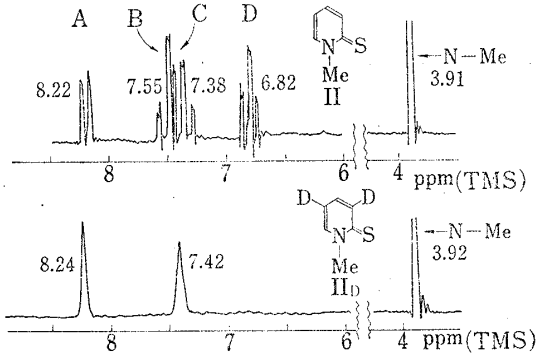

Fig. 1. NMR Spectra of II and II_D (in Me_2SO-d_6) (100 MHz)

1) Part XVI: H. Tomisawa and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **21**, 2585 (1973).
2) Location: *Komatsushima, Sendai.*
3) H. Tomisawa, H. Hongo, H. Kato, and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **19**, 2414 (1971).
4) H. Tomisawa, Y. Kobayashi, H. Hongo, and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 932 (1970).
5) A. Gutbier, *Ber.*, **33**, 3359 (1900).
6) J. Renault, *Ann. Chim.*, **10**, 135 (1955).

determined in order to ascertain the substituent position in its reaction products. The NMR spectra of several alkyl derivatives of thiopyridone were reported by Bauer and others,[7] but that of II was not reported. Therefore, the unequivocal confirmation of NMR assignment of II was required, and was given by comparison with NMR spectrum of II and that of its dideuterio derivative, *i.e.*, 3,5-dideuterio-1-methyl-2(1*H*)-thiopyridone (II_D). II_D was prepared by treatment with 3,5-dideuterio-1-methyl-2(1*H*)-pyridone (I_D)[8] and phosphorus pentasulfide in a good yield. The NMR spectrum (in Me_2SO-d_6) of II_D is shown in Fig. 1. By designating the signals for each H in the NMR spectrum of II (Fig. 1) optionally as A, B, C, and D from the lowest magnetic field and considering the *ortho*-coupling alone, the signals A and B are doublet and they would be assigned to the protons at 3- and 6-positions. C and D are each triplets and would be assigned to the protons at 4- and 5-positions. It is not possible from this spectrum alone to determine whether A should be assigned to the proton at 3- or 6-position but comparison of this spectrum with that of II_D, in which only the protons at 4- and 6-positions are present, would make it possible to assign the signals in the spectrum of II. The chemical shift of signal A agrees approximately with that of the proton at 6-position in lower magnetic field of II_D, and signal A can therefore be assigned to the proton at 6-position. Signal B must be assigned to the proton at 3-position. Assignment of signals C and D can be made similarly. The signal C, whose chemical shift agrees approximately with that of the signal in the higher magnetic field in the NMR spectrum of II_D is therefore assigned to the proton at 4-position. Consequently, signal D must be assigned to the proton at 5-position. Thus, the signals in the NMR spectrum of II (in Me_2SO-d_6) have been assigned from lower magnetic field to protons at 6 (8.22 ppm), 3 (7.55 ppm), 4 (7.38 ppm), and 5 (6.82 ppm) positions. The signals in the NMR spectrum of I in Me_2SO-d_6 can be assigned to protons in 6 (7.31 ppm), 4 (7.26 ppm), 3 (6.57 ppm), and 5 (6.15 ppm) positions. It was found by this means that the 3-H signal in the sulfur compound (II) has shifted greatly to a lower magnetic field compared with that in the oxygen compound (I), which is an interesting phenomenon.

A mixture of II, paraformaldehyde, conc. hydrochloric acid, and phosphoric acid was heated in an oil bath of 130° for 72 hr, sodium acetate and acetic anhydride were added, and the mixture was heated at 130° for further 3 hr. Aftertreatment gave two kinds of crystals (IV and V) and a trace of oil besides recovery of II (40%). IV formed yellow needles, mp 111—112.5°, and its analytical values corresponded to C_7H_9ONS, II with introduction of one hydroxymethyl group. Yield, 22%. The NMR spectrum of IV (in Me_2SO-d_6), as shown in

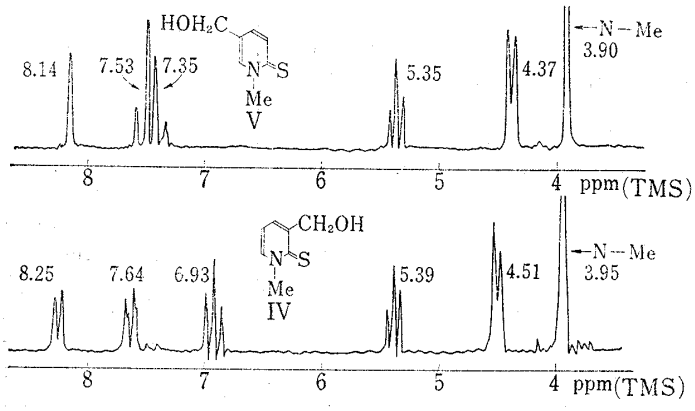

Fig. 2. NMR Spectra of IV and V (in Me_2SO-d_6) (100 MHz)

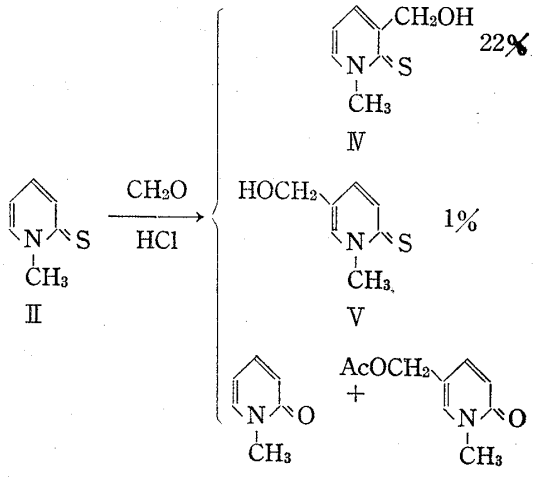

Chart 2

7) L. Bauer, G.E. Wright, B.A. Mikrut, and C.L. Bell, *J. Heterocyclic. Chem.*, **2**, 447 (1965).
8) Y. Kawazoe and Y. Yoshioka, *Chem. Pharm. Bull.* (Tokyo), **16**, 715 (1968).

Fig. 2, indicated the presence of a hydroxymethyl group with a doublet and a triplet signals with a coupling constant of 5 Hz in the higher magnetic field, while two doublets and one triplet in the lower field indicated from their coupling constants that the three protons on the ring are adjacent to each other. Further, the chemical shift of the signal in the lowest magnetic field agrees approximately with that of the signal in the lowest magnetic field, *i.e.*, 6-H, in the NMR spectrum of II. Consequently, the three protons in the ring of IV would be present in adjacent 6-, 5-, and 4-positions. This means that the structure of IV would be 3-hydroxymethyl-1-methyl-2(1*H*)-thiopyridone. V formed pale yellow needles of mp 109—110°, C_7H_9ONS, corresponding to the introduction of one hydroxymethyl group into II. Yield, 1%. The NMR spectrum of V (in Me_2SO-d_6) (Fig. 2) also exhibited signals due to hydroxymethyl in higher magnetic field, similar to that of IV, while the ring protons appear as one singlet and two doublets in a lower field. The chemical shift of the singlet signal is approximately the same as that of the signal for 6-H in the NMR spectrum of II, and the two adjacent protons must be at 3- and 4-positions. Consequently, the structure of V would be 5-hydroxymethyl-2(1*H*)-thiopyridone. The oil obtained in a trace amount was distilled in high vacuum. From the comparison of infrared (IR) spectra, the fraction that distilled out at 0.1 Torr and bath temperature of *ca.* 80° was identified as I, and the fraction that distilled out at 0.1 Torr and bath temperature of *ca.* 150° as 5-acetoxymethyl-1-methyl-2(1*H*)-pyridone[4] synthesized by another route. These compounds are considered to be formed by hydrolysis of II and, therefore, II was heated with conc. hydrochloric acid at 130° for 72 hr, from which about 20% of I was obtained with about 80% recovery of II. Hydrolysis of II progresses more rapidly in basic solution and heating of II with 5N sodium hydroxide under the same conditions produced 86% of I. The foregoing is the condition for the reaction of II with formaldehyde and hydrochloric acid giving the product in the best yield. The treatment with sodium acetate and acetic anhydride was the same as the post-treatment for the same reaction of I.[4] For some unknown reason, the yield becomes markedly low if this treatment is omitted. As shown above, the reaction of II with formaldehyde and hydrochloric acid results in the main production of 3-substituted product. It was found from this experiment that the same reaction of I gives only the 5-substituted product and that II gives the product only under a more drastic condition than in the case of I.

Experimental[9]

3,5-Dideuterio-1-methyl-2(1*H*)-thiopyridone (II_D)——A mixture of 1.5 g of 3,5-dideuterio-1-methyl-2(1*H*)-pyridone[8] (I_D) and 3.3 g of P_2S_5 was heated at a bath temperature of 130° for 5 hr, cooled, basified with NaOH solution, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, $CHCl_3$ was evaporated under a reduced pressure, and the residue was recrystallized from H_2O to II_D as pale yellow plates, mp 88—89°. Yield, 1.47 g (86%). *Anal.* Calcd. for $C_6H_5O_2NS$: N, 11.02. Found: N, 10.98. NMR (in Me_2SO-d_6) ppm: 3.92 (3H, singlet, N-CH_3), 7.42 (1H, singlet, C4-H), 8.24 (1H, singiet, C6-H).

Reaction of 1-Methyl-2(1*H*)-thiopyridone (II) with Formaldehyde and Hydrochloric Acid——A mixture of 5 g of II, 5 g of $(CH_2O)_n$, 20 g of conc. HCl, and 5 ml of H_3PO_4 was heated at a bath temperature of 130° for 72 hr, 46 g of $AcONa \cdot 3H_2O$ and 8.2 g of Ac_2O were added, and the mixture was heated for further 3 hr at the same temperature. When cooled, the reaction mixture was basified with K_2CO_3 and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, $CHCl_3$ was evaporated under a reduced pressure, and reddish yellow oily residue thereby obtained was submitted to column chromatography over silica gel (Kieselgel Merck, 0.05—0.2 mm, 70—325 mesh). The fraction eluted with benzene–acetone (49: 1) affored 2.0 g (40%) of the recovered II. The solvent was evaporated from the fraction eluted with benzene-acetone (19: 1) and the residue was recrystallized from benzene to 1.4 g (22%) of 3-hydroxymethyl-1-methyl-2(1*H*)-thiopyridone (IV) as yellow needles, mp 111—112.5°. *Anal.* Calcd. for C_7H_9ONS: C, 54.19; H, 5.85; N, 9.03. Found: C, 53.99; H, 5.97; N, 9.11. IR ν_{max}^{Nujol} cm^{-1}: 3300, 3180 (ν_{OH}), 1060 (δ_{CO}), 770 (δ_{CH}). NMR (in Me_2SO-d_6) ppm: 3.95 (3H, singlet, N-CH_3), 4.51 (2H, doublet, J=5 Hz, -C<u>H</u>$_2$OH), 5.39 (1H, triplet, J=5 Hz, -CH_2O<u>H</u>), 6.93 (1H, triplet, J=7 Hz, C5-H), 7.64 (1H, quartet, J=7 Hz, J=2 Hz, C4-H), 8.25 (1H, broad doublet, J=7 Hz, C6-H). UV λ_{max}^{EtOH} nm (log ε): 210 (4.12), 280 (4.08), 353 (3.90).

9) All melting points were uncorrected.

The earlier portion of the fraction eluted with benzene–acetone (4: 1) was evaporated under a reduced pressure and the residue was recrystallized from benzene–acetone (9: 1) to 65 mg (1%) of 5-hydroxymethyl-1-methyl-2(1*H*)-thiopyridone (V) as pale yellow needles, mp 109—110°. *Anal.* Calcd. for C_7H_9ONS: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.01; H, 5.98; N, 9.18. IR ν_{max}^{Nujol} cm^{-1}: 3250 (ν_{OH}), 1050 (δ_{CO}), 880 (δ_{CH}). NMR (in Me_2SO-d_6) ppm: 3.90 (3H, singlet, N-CH_3), 4.37 (2H, doublet, J=5 Hz, -CH_2OH), 5.35 (1H, triplet, J=5 Hz, -CH_2O<u>H</u>), 7.35 (1H, quartet, J=7.5 Hz, J=2.5 Hz, C4-H), 7.53 (1H, doublet, J=7.5 Hz, C3-H), 8.14 (1H, broad singlet, C6-H). UV λ_{max}^{EtOH} nm (log ε): 210 (4.10), 288 (4.20), 360 (3.92).

The latter part of the eluate with benzene–acetone (4: 1) afforded a minute amount of brown oil. Low-pressure distillation of this oil gave 1-methyl-2(1*H*)-pyridone (I), bp *ca.* 80° (bath temp.)/0.1 Torr, and 5-acetoxymethyl-1-methyl-2(1*H*)-pyridone, bp *ca.* 150° (bath temp.)/0.1 Torr.

Besides the above reaction conditions (a) which gave the highest yield of the products, other reaction conditions were tried. (b) The quantity of II, $(CH_2O)_n$, and conc. HCl was the same as in (a) but H_3PO_4 was omitted. The mixture was heated at 130° for 3 hr and after-treatment the same as in (a). The starting material (II) was recovered in 98.7%. (c) Glacial AcOH was added to the same formula as in (a), the mixture was heated at 130° for 10 hr, and after-treatment as in (a). Recovery of II. 86%, yield of IV 7%, and of V 1.6%. (d) The same reaction mixture as in (a) was heated for 24 hr and gave 70% of II, 5% of IV, and 1.7% of V. (e) A solution of II and $(CH_2O)_n$ in EtOH was bubbled with dry HCl and II was recovered. (f) Ac_2O was added to the formula of (a) and the mixture was heated at 130° for 24 hr, resulting in the formation of 71% of II, 9% of IV, and 1% of V. (g) The same reaction mixture as (f) was heated for 72 hr by which 47% of II and 20% of IV were obtained, with detection of a trace of V by thin-layer chromatography.

Hydrolysis of 1-Methyl-2(1*H*)-thiopyridone (II) with Hydrochloric Acid——A mixture of 1 g of II and 7.5 g of conc. HCl was heated at a bath temperature of 130° for 72 hr, cooled, basified with K_2CO_3, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, $CHCl_3$ was evaporated under a reduced pressure, and the residue was chromatographed over silica column. Fraction eluted with benzene–acetone (49: 1) afforded 0.775 g (77.5%) of recovered II and the acetone eluate gave 0.173 g (19.8%) of I.

Hydrolysis of 1-Methyl-2(1*H*)-thiopyridone with Sodium Hydroxide——A mixture of 1 g of II and 20 ml of 5N NaOH was heated at a bath temperature of 130° for 72 hr and the cooled mixture was extracted with $CHCl_3$. The product obtained by extraction with $CHCl_3$ was purified by silica gel chromatography and 0.753 g (86.4%) of I was obtained.

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