[Chem. Pharm. Bull. 12 (5) 595 ~ 601]

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85. Renzo Dohmori : Rearrangement of Sulfonamide Derivatives. VII.[*1] Rearrangement Reaction of the Sulfonamide Derivatives of Pyridine 1-Oxide at a Room Temperature.

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It has been shown previously that *o*- and *p*-nitrobenzenesulfonamide derivatives undergo rearrangement in the presence of alkali accompanied with the liberation of sulfur dioxide to form *o*- and *p*-phenylacetamide derivatives.[1,2] It was subsequently extended to heterocyclic compounds, such as 2- and 4-sulfonamide derivatives of pyridine and quinoline 1-oxides.[3,4]

In further studies of this rearrangement and in connection with kinetic studies, which will be reported in a following paper, it was desirable to know the reaction products at a room temperature. Nitrobenzenesulfonamide derivatives underwent the rearrangement in alkaline solution to nitrophenylacetamides in good yields at a room temperature. However, in the previous paper[3] the reaction of pyridinesulfonamide 1-oxide derivatives had not been carried out at a room temperature.

N-acetoacetyl-2-pyridinesulfonamide 1-oxide (I) evolved ammonia in 10% sodium hydroxide at 24° and gave colorless prisms A, m.p. 188~189°, and colorless prisms B, m.p. 204~206° (decomp.) by acidification.

Reaction of B with 10% sodium hydroxide on the steam bath resulted in the formation of 2-pyridineacetic acid 1-oxide (Ⅳ) by evolution of ammonia. Ⅳ was decarboxylated at 127° to 2-picoline 1-oxide which exhibited no melting point depression and whose infrared spectrum was identical with an authentic sample. These results and the elemental analysis indicated that B is 2-pyridineacetamide 1-oxide (Ⅲ).

On the other hand, the elemental analysis and molecular weight determination by Rast method showed that A possessed the empirical formula $C_9H_7O_2N$, which corresponded the loss of one mole of ammonia from *α*-acetyl-2-pyridineacetamide 1-oxide (Ⅱ). This compound was very stable and did not react with 10% hydrochloric acid on the steam bath for half an hour, but the crystals gradually became yellow in sunlight. Refluxing a solution of A in 20% hydrochloric acid for one hour gave 2-pyridineacetic acid 1-oxide (Ⅳ) and heating with concentrated ammonium hydroxide in glass tube at 120° for three hours afforded Ⅲ. A give a positive hydroxamic acid test and the test solution was chromatographed on paper (solvent system : BtOH-AcOH-H_2O=4:1:5). There were two spots, the smaller (Rf 0.32) was identified as 2-pyridineacetohydroxamic acid 1-oxide and the other (Rf 0.52) as acetohydroxamic acid. This suggested that A consisted of an acetyl and a 2-pyridineacetyl 1-oxide group.

All of the experimental results given thus far are consistent with the properties of 3-acetyl-2*H*-isoxazolo[2,3-*a*]pyridin-2-one (Ⅴ) reported by Adams.[5] The identity of Ⅴ was established by comparison with an authentic sample synthesized by his procedure. It was assumed that A was produced by the loss of ammonia from the intermediate, *α*-acetyl-2-pyridineacetamide 1-oxide, or dehydration from *α*-acetyl-2-pyridineacetic acid 1-oxide. The yields of A and B were 42.8 and 56.8% respectively.

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*1 Part Ⅵ. R. Dohmori : This Bulletin, **12**, 591 (1964).

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1) T. Naito, R. Dohmori, O. Nagase : Yakugaku Zasshi, **74**, 593 (1954).
2) T. Naito, R. Dohmori, M. Sano : *Ibid.*, **74**, 596 (1954).
3) T. Naito, R. Dohmori : This Bulletin, **3**, 38 (1955).
4) T. Naito, R. Dohmori, T. Kotake : *Ibid.*, **12**, 588 (1964).
5) R. Adams, W. Reifschneider : J. Am. Chem. Soc., **79**, 2236 (1957).

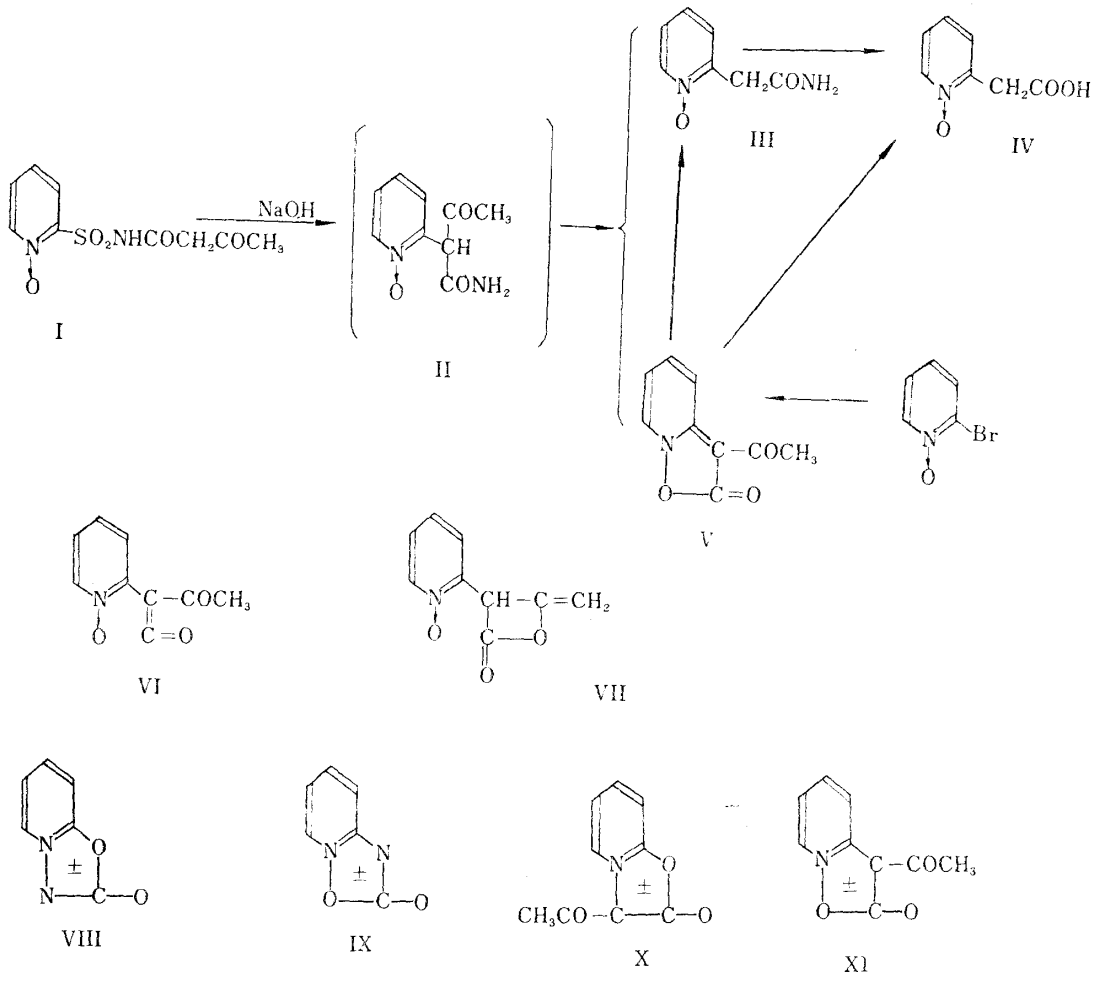

Chart 1.

Further discussion of the structure of V follows below. Although A was also assumed to be represented by structure (VI or VII), this assumption was not acceptable, since A was unchanged on treatment with water or alcohol. Other evidence is given by the infrared spectrum. It showed an intense absorption band at 1747 cm^{-1}, which was assigned to an isoxazolone-C=O differing from those of ketene[6] and ketene dimer.[7]

Hoegerle[8] discussed the similarity of the absorption spectra of *meso*-ionic 8*aH*-[1,3,4]oxadiazolo[3,2-*a*]pyridin-2(3*H*)-one (VIII) and 2*H*-[1,2,4]oxadiazolo[2,3-*a*]pyridin-2-one (IX),[9] and now the same comparative studies were done with A and *meso*-ionic 3-acetyl-8*aH*-oxazolo[3,2-*a*]pyridin-2(3*H*)-one (X).*[3,10] As shown in Fig. 1, the infrared spectrum of A strongly resembles X, especially the stretching-vibration band of the carbonyl group. Also the ultraviolet spectra were similar, cf. Fig. 2. The relative stability of this compound reflects V of the structure is only one of several contributors to a resonance hybrid. This compound may preferably be represented as XI in which sextets

*[3] This compound (m.p. 170~171°) was synthesized by the procedure of A. Lawson but the ultraviolet spectrum was slightly different. Lawson's 4-propionyl derivative (m.p. 146~147°) was also synthesized and the same difference in the ultraviolet spectrum was observed although the melting points of the respective compounds were identical.

6) L. G. Drayton, H. W. Thompson: J. Chem. Soc., **1948**, 1416.
7) D. H. Whiffen, H. W. Thompson: *Ibid.*, **1946**, 1005.
8) K. H. Hoegerle: Helv. Chim. Acta, **41**, 548 (1958).
9) A. R. Katritzky: J. Chem. Soc., **1956**, 2063.
10) A. Lawson, D. H. Miles: *Ibid.*, **1959**, 2865.

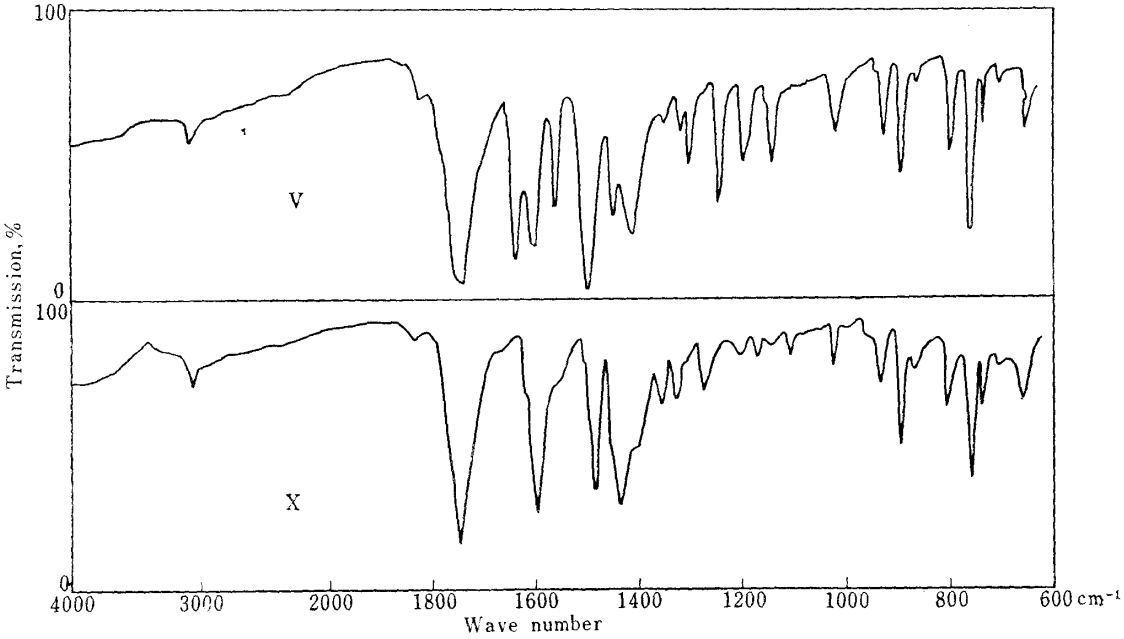

Fig. 1. Infrared Spectra

of electrons are associated with both rings rather than as V in a classical formulation.

Treatment of N-phenylacetyl-2-pyridinesulfonamide 1-oxide (XII) with 10% sodium hydroxide at 36° for twenty hours, gave colorless crystals, m.p. 102° (decomp.) in 79% yield and yellow leaflets, m.p. 148° (decomp.) in 6.7% yield. The former was identified as α-phenyl-2-pyridineacetic acid 1-oxide (XIII) by mixed melting point with an authentic sample[4] and by its infrared spectrum.

The latter was insoluble in dilute acid or alkaline solution, and turned brown in sunlight. Heating this compound with 20% hydrochloric acid, yielded 2-benzylpyridine

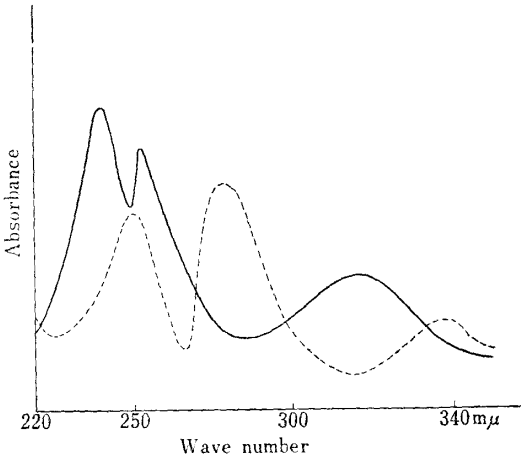

Fig. 2. Ultraviolet Spectra
——— X ----- V

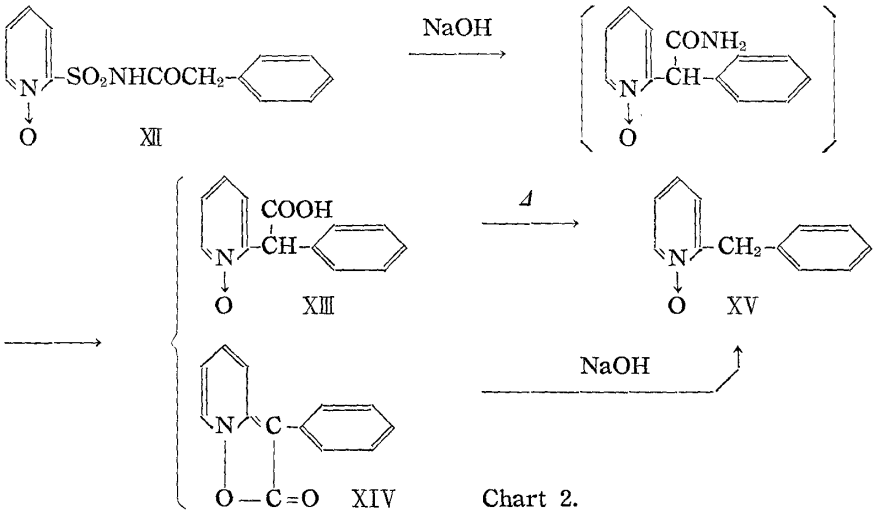

Chart 2.

1-oxide (XV). The structure of XIV was established by analysis ($C_{13}H_9O_2N$) and the presence of an isoxazolone-C=O band at 1715 cm^{-1} in the infrared spectrum.

A new compound, N-cyanoacetyl-2-pyridinesulfonamide 1-oxide (XVI), synthesized by way of N-chloroacetyl derivative from pyridinesulfonamide 1-oxide, was reacted with 10% sodium hydroxide at 95° and 20°, respectively.

At 95° it gave colorless prisms, m.p. 126° (decomp.), which were identified as 2-pyridineacetic acid 1-oxide (IV).

At 20° for one hour, the reaction mixture gave colorless crystals, m.p. 180° (decomp.), whose elemental analysis fitted the empirical formula $C_8H_7O_2N_3 \cdot HCl$. Neutralization of this hydrochloride with sodium bicarbonate generated a free base C in 70.7% yield, which was recrystallized from methanol as yellow prisms, m.p. 148° (decomp.). Heating C with 10% sodium hydroxide produced an ammonical odor while its acidification afforded 2-pyridineacetic acid 1-oxide (IV). Adams[5] reported that the condensation of 2-bromo-6-methylpyridine 1-oxide (XIX) and ethyl sodiocyanoacetate gave ethyl 2-imino-7-methyl-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (XX) and 2-oxo-7-methyl-2*H*-isoxazolo[2,3-*a*]pyridin-3-carbonitrile (XXI). From his report and the rearrangement results of other sulfonamide derivatives, it was presumed that the structure of C is represented by either XVII or XVIII. Since C shows the presence of an amido-C=O band, but no nitrile band in infrared spectrum, XVIII is the preferred structure. In addition, C was separated as a hydrochloride which is inconsistent with XVII.

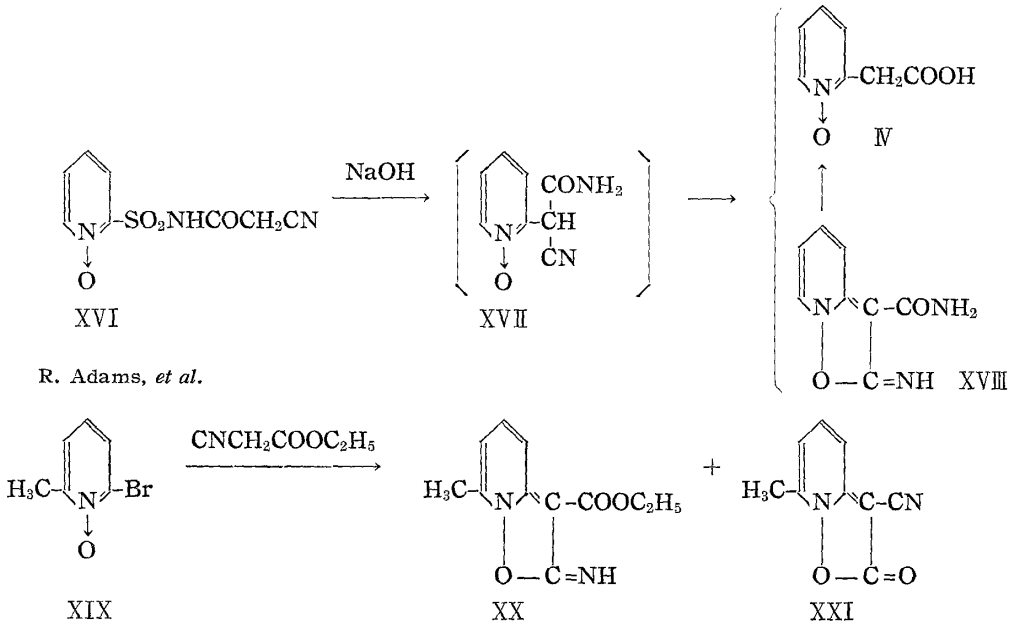

Chart 3.

N-acetoacetyl-4-pyridinesulfonamide 1-oxide (XXII) was treated with 10% sodium hydroxide at 20° for half an hour. Colorless needles, m.p. 144~145° (decomp.) in 8.9% yield, and colorless prisms, m.p. 180° (decomp.) in 78.8% yield were obtained. The former was identified as 4-pyridineacetic acid 1-oxide (XXIII) by mixed melting point and its infrared spectrum. The latter was converted into 4-pyridineacetic acid 1-oxide in 10% sodium hydroxide solution with evolution of ammonia. This compound was confirmed as 4-pyridineacetamide 1-oxide (XXIV) from its elemental analysis and infrared spectrum.

Treatment of N-phenylacetyl-4-pyridinesulfonamide 1-oxide (XXV) with 10% sodium hydroxide at 27° for twelve hours afforded colorless crystals, m.p. 98~99° (decomp.),

84.8% yield, which were identified as α-phenyl-4-pyridineacetic acid 1-oxide (XXVI) by mixed melting point and its infrared spectrum.

The 4-pyridinesulfonamide derivatives, however, did not give those "non-benzenoid aromatic compounds," as in the case of 2-pyridinesulfonamide derivatives prepared by the same procedure.

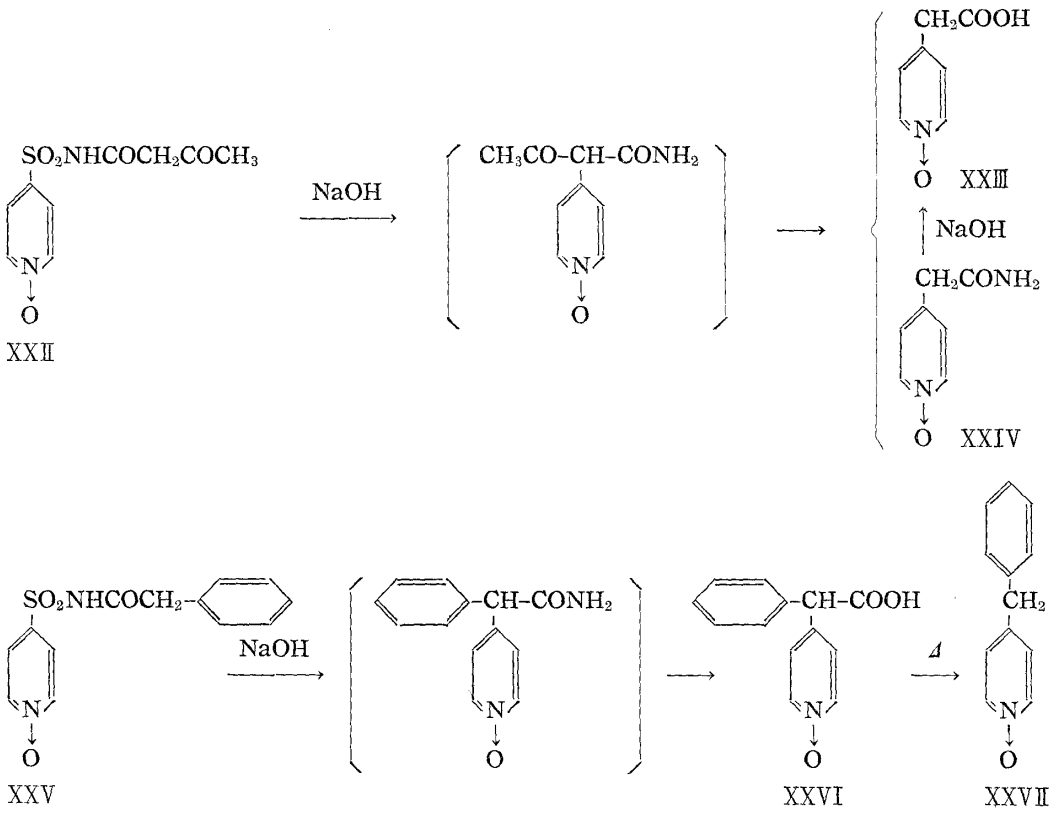

Chart 4.

Experimental*4

Rearrangement Reaction of N-Acetoacetyl-2-pyridinesulfonamide 1-Oxide (I). Formation of III and V——A mixture of I (5.2 g.) in 10% NaOH (40 ml.) was kept at 24° for 1 hr., adjusted to pH 2.0 with 10% HCl, and concentrated to 30 ml. *in vacuo*. The crystals (1.6 g.) were obtained by filtration and the filtrate was evaporated to dryness *in vacuo* and the residue was extracted with abs. EtOH. After removing the solvent *in vacuo*, the residue was treated with H_2O (10 ml.), and the crystals (0.5 g.) were filtered and added to the first crops. The crystals (2.1 g. of 57.8%) were recrystallized from MeOH to colorless prisms (V), m.p. 188~189°. *Anal.* Calcd. for $C_9H_7O_3N$: C, 61.02; H, 3.98; N, 7.91; mol. wt., 177. Found : C, 61.14; H, 4.01; N, 7.81; mol. wt. (Rast method : using camphor), 181. IR ν_{max}^{KBr} cm^{-1} : 1747 (isoxazolone-C=O), 1652 (acetyl). UV λ_{max}^{EtOH} mμ (log ε) : 250 (4.13), 281 (4.20), 349 (3.84). The identification of this compound with 3-acetyl-2*H*-isoxazolo[2,3-*a*]pyridin-2-one was confirmed by mixed melting point and the comparison of IR spectrum. An authentic sample was synthesized by Adams's procedure.

The mother liquors from V were evaporated to dryness *in vacuo* and the residue was treated with EtOH (4 ml.). The crystals were collected and recrystallized from MeOH to 1.3 g. (42.8%) of colorless prisms, m.p. 204~206° (decomp.). *Anal.* Calcd. for $C_7H_8O_2N_2$: C, 55.25; H, 5.30; N, 18.41. Found : C, 55.25; H, 5.38; N, 18.51.

This substance (140 mg.) was heated with 10% NaOH (2 ml.) on a steam bath (90~95°) for 30 min., and the solution was adjusted to pH 2.0 with 10% HCl, concentrated *in vacuo*. The obtained crystals were recrystallized from MeOH to colorless prisms, m.p. 126~127° (decomp.), which showed no depression by admixture with 2-pyridineacetic acid 1-oxide and the IR spectra of the two were completely identical.

*4 All melting points are uncorrected.

Rearrangement Reaction of N-Phenylacetyl-2-pyridinesulfonamide 1-Oxide (XII). Formation of XIII and XIV——A solution of XII (1.5 g.) in 10% NaOH (10 ml.) was kept at 36° for 20 hr., adjusted to pH 2.0 with 10% HCl. The colorless crystals (0.8 g. or 77.8%) were precipitated with liberation of SO_2. This substance, m.p. 102° (decomp.) gave no depression of melting point by admixture with α-phenyl-2-pyridineacetic acid 1-oxide (XIII) and the IR spectra of the two were identical.

The pale yellow mother solution of XIII, was allowed to stand for 2 days in the dark room to give crystals (XIV). Recrystallization from EtOH gave yellow leaflets, m.p. 148° (decomp.). *Anal.* Calcd. for $C_{13}H_9O_2N$: C, 73.99; H, 4.30; N, 6.63. Found: C, 73.85; H, 4.31; N, 6.70. IR ν_{max}^{KBr} cm^{-1}: 1704 (isoxazolone-C=O). UV λ_{max}^{EtOH} mμ (log ε): 266 (3.24), 305 (3.40), 388 (2.80).

A solution of XIV (40 mg.) in 20% HCl (5 ml.) was heated at 100~110° for 1 hr., and then evaporated to dryness *in vacuo*. The product gave a picrate, the pale yellow needles, m.p. 121~122°. This picrate was undepressed by admixture with the picrate of 2-benzylpyridine 1-oxide.

N-Chloroacetyl-2-pyridinesulfonamide 1-Oxide——Monochloroacetyl chloride (7.5 g.) was added dropwise under stirring to a solution of 2-pyridinesulfonamide 1-oxide (3.5 g.) in 10% Na_2CO_3 (70 ml.) at below 3°. The reaction mixture was allowed to stand for 1 hr. and insoluble materials were filtered off. The filtrate was adjusted to pH 2.0 with 10% HCl, and the precipitated product was recrystallized from MeOH to colorless plates, m.p. 159~160° (decomp.). Yield, 2.0 g. (40%). *Anal.* Calcd. for $C_7H_7O_4N_2SCl$: C, 33.54; H, 2.82; N, 11.18. Found: C, 33.72; H, 2.92; N, 11.33.

N-Cyanoacetyl-2-pyridinesulfonamide 1-Oxide (XVI)——A mixture of N-chloroacetyl derivative (6 g.) in 15% Na_2CO_3 (8 ml.) and 30% NaCN (6 ml.) was allowed to stand overnight at a room temperature. The reaction mixture was acidified with HCl, the precipitated crystals were recrystallized from MeOH to colorless leaflets, m.p. 170° (decomp.). Yield, 3.5 g. (60.2%). *Anal.* Calcd. for $C_8H_7O_4N_3S$: C, 39.83; H, 2.93; N, 17.42. Found: C, 39.91; H, 2.89; N, 17.57. IR ν_{max}^{KBr} cm^{-1}: 2250 (CN).

Rearrangement Reaction of N-Cyanoacetyl-2-pyridinesulfonamide 1-Oxide (XVI). Formation of IV and XVIII——1) At 90~95°: A mixture of XVI (480 mg.) in 10% NaOH (4 ml.) was heated on a steam bath (90~95°) for 1 hr., and acidified solution with HCl was evaporated to dryness *in vacuo*. The residue was extracted with abs. EtOH. The extract was concentrated to a small volume *in vacuo* and the colorless crystals were filtered. This substance was identified with 2-pyridineacetic acid 1-oxide by its failure to depress the melting point of admixture and by its IR spectrum.

2) At 25°: A solution of XVI (480 mg.) in 10% NaOH (4 ml.) was kept at 20° for 1 hr., and acidified with HCl. The precipitated material was recrystallized from MeOH to colorless prisms, m.p. 180° (decomp.). Yield, 300 mg. (70.7%). *Anal.* Calcd. for $C_8H_7O_2N_3 \cdot HCl$: C, 44.98; H, 3.77; N, 19.66. Found: C, 45.05; H, 3.51; N, 20.01. A solution of this hydrochloride was neutralized with sodium bicarbonate, and the precipitate was recrystallized from MeOH to yellow prisms, m.p. 140° (decomp.). *Anal.* Calcd, for $C_8H_7O_2N_3$: C, 54.23; H, 3.98; N, 23.72. Found: C, 53.95; H, 4.20; N, 23.93. IR ν_{max}^{KBr} cm^{-1}: 3270, 3210, 3120 (-NH), 1672, 1640 ($-CONH_2$). UV λ_{max}^{EtOH} mμ (log ε): 301 (4.05), 380 (3.73).

Rearrangement Reaction of N-Acetoacetyl-4-pyridinesulfonamide 1-Oxide (XXII). Formation of XXIII and XXIV——XXII (1.5 g.) was treated with 10% NaOH (10 ml.) at 20° for 30 min., the reaction mixture was brought to pH 2.2 with HCl, and evaporated to dryness *in vacuo*. The residue was extracted with abs. EtOH. The EtOH was removed and the residue was dissolved in H_2O (80 ml.). The solution that was adjusted to pH 7.0 was applied on a Diaion SA-100 ion-exchange resin (100~200 mesh, chloride form) bed (20 cm. long, 1 cm. diameter), and the effluent was evaporated to dryness *in vacuo*. The residue was extracted with abs. EtOH, the extract was concentrated *in vacuo*, and the separated crystals were filtered. Recrystallization of this substance from EtOH gave 700 mg. (78.8%) of colorless prisms, m.p. 180° (decomp.). *Anal.* Calcd. for $C_7H_8O_2N_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 54.85; H, 5.57; N, 18.21. Heating of this substance with 10% NaOH on the steam bath for 30 min., resulted in the evolution of ammonia odor while its acidification with HCl gave colorless crystals, m.p. 144~145° (decomp.) which were identified with 4-pyridineacetic acid 1-oxide by mixed melting point and by its IR spectrum.

The column was washed with 0.2*M* HCl (1.5 L.), and the effluent was evaporated to dryness *in vacuo*. The residue was extracted with abs. EtOH, the extract was concentrated *in vacuo*, and the obtained crystals were collected. The product, colorless prisms, m.p. 144~145° (decomp.), recrystallized from EtOH was proved to be identical with 4-pyridineacetic acid 1-oxide by mixed melting point and its IR spectrum. Yield, 80 mg. (8.9%).

Rearrangement Reaction of N-Phenylacetyl-4-pyridinesulfonamide 1-Oxide (XXV). Formation of XXVI——A solution of XXV (1.5 g.) in 10% NaOH (10 ml.) was allowed to stand at 27° for 17 hr., and acidified with HCl to give the colorless needles. Yield, 1.0 g. (84.8%). This substance was identified with α-phenyl-4-pyridineacetic acid 1-oxide by mixed melting point and by IR spectrum.

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The author is grateful to Dr. T. Naito, Subdirector of this Laboratory for his kind and unfailing guidance, and to Dr. A. Okano for valuable discussion and suggestions during the course of this work. The author wishes also to thank Mr. B. Kurihara and Miss K. Hanawa for elemental analyses.

Summary

The rearrangement reaction products of N-acetoacetyl, N-phenylacetyl, and N-cyanoacetyl derivatives of 2- and 4-pyridinesulfonamide 1-oxides with 10% sodium hydroxide at a room temperature were studied and their structures were confirmed.

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86. Renzo Dohmori : Rearrangement of Sulfonamide Derivatives. VIII.*1 Kinetics of the Rearrangement Reaction of Sulfonamide Derivatives with Alkali.

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In the previous paper[1] of this series, certain deductions were made about the reaction mechanism of a rearrangement of N-substituted sulfonamide derivatives in the presence of alkali and this reaction was presumed to be an intramolecular rearrangement.

The present paper deals with the determination of the rate coefficients of ten kinds of sulfonamide derivatives and the discussion of the electronic and steric effects of N-substituents of nitrobenzenesulfonamide and pyridinesulfonamide 1-oxides. The reaction mechanism of this rearrangement is described.

The reactions of their sulfonamides with alkali were consecutive reactions, as described in the preceding paper. However, the reaction rates of the rearrangement could be measured by means of quantitative analysis of sulfur dioxide liberated from that step. In the present series of experiments, large excess aqueous sodium hydroxide solution was used to keep the OH^- concentration constant.

Reactants

N-Acetoacetyl-*p*-nitrobenzenesulfonamide[2]——*p*-Nitrobenzenesulfonamide was reacted with ketene dimer. The product was recrystallized from EtOH to pale yellow needles, m.p. 136°.

N-Acetoacetyl-*o*-nitrobenzenesulfonamide[2]——This compound was obtained from *o*-nitrobenzenesulfonamide as described above and recrystallized from EtOH to pale yellow needles, m.p. 118~119°.

N-Cyanoacetyl-*p*-nitrobenzenesulfonamide[3]——N-Chloroacetyl-*p*-nitrobenzenesulfonamide obtained from *p*-nitrobenzenesulfonamide with chloroacetyl chloride was converted into the corresponding N-cyanoacetyl derivative with NaCN. Recrystallization from EtOH gave pale yellow needles, m.p. 207~209°.

*1 Part Ⅶ. R. Dohmori : This Bulletin, **12**, 595 (1964).

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1) T. Naito, R. Dohmori, M. Shimoda : This Bulletin, **3**, 34 (1955).

2) S. Petersen : Chem. Ber., **83**, 55 (1950).

3) T. Naito, R. Dohmori, M. Sano : Yakugaku Zasshi, **74**, 596 (1954).