

10. Takeo Naito and Renzo Dohmori : Rearrangement of Sulfonamide Derivatives. IV.¹⁾ Rearrangement Reaction of the Sulfonamide Derivatives of Pyridine and Quinoline 1-Oxides.

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It has been shown previously²⁾ that *p*- and *o*-nitrobenzenesulfonamide derivatives undergo rearrangement in alkaline solution to form *p*- and *o*-phenylacetamide derivatives.

In the present series of experiments, this rearrangement reactions were examined with 2- and 4-sulfonamide derivatives of pyridine, picoline, and quinoline 1-oxides and it was found that the reaction proceeded exactly the same as in the case of nitrobenzene and that pyridine-, picoline-, and quinoline-acetic acid 1-oxides were formed. It is thereby learned that this rearrangement reaction can also be applied to heterocyclic compounds.

The 2- and 4-sulfonamide derivatives of pyridine, picoline, and quinoline 1-oxides were prepared in the following manner. 2-Bromopyridine and thiourea were reacted to form thiuronium salt, which was decomposed with ammonia to 2-mercaptopyridine,³⁾ derived to the sulfochloride by bubbling chlorine gas through its hydrochloric acid solution, aminated to 2-pyridinesulfonamide, and finally derived to its 1-oxide with hydrogen peroxide in glacial acetic acid as 2-pyridinesulfonamide 1-oxide, m.p. 228°. 4-Methyl-2-pyridinesulfonamide 1-oxide, m.p. 222~223°, was prepared by the same manner from 2-mercapto-4-methylpyridine. 4-Pyridinesulfonamide 1-oxide, m.p. 228°(decomp.), and 4-quinolinesulfonamide 1-oxide, m.p. 228°(decomp.), were prepared by the foregoing method respectively from 4-mercaptopyridine 1-oxide⁴⁾ and 4-mercaptoquinoline 1-oxide.⁴⁾ Attempt was made to prepare a sulfonamide derivative from 2-mercaptoquinoline⁵⁾ but the passage of chlorine gas through its hydrochloric acid solution resulted in the formation of 2-chloroquinoline in 76.4% yield and its sulfochloride could not be obtained by this means.

Application of ketene dimer to each of the sulfonamide derivatives thereby obtained yielded 2-(N-acetoacetyl)pyridinesulfonamide 1-oxide (I), m.p. 152~153°(decomp.), 4-methyl-2-(N-acetoacetyl)pyridinesulfonamide 1-oxide (VI), m.p. 153~154°(decomp.), 4-(N-acetoacetyl)pyridinesulfonamide 1-oxide (IX), m.p. 183~184°(decomp.), and 4-(N-acetoacetyl)quinolinesulfonamide 1-oxide (XII), m.p. 172~173°(decomp.).

The rearrangement reaction was then examined with these synthesized compounds. Heating of (I) with 10% sodium hydroxide at 90~95° resulted in evolution of ammonia odor while its acidification with hydrochloric acid generated a strong odor of sulfur dioxide, suggesting the occurrence of the rearrangement reaction. The treatment of the reaction mixture yielded colorless needles, m.p. 125~126°(decomp.), whose elemental analytical values corresponded to those of 2-pyridine-acetic acid 1-oxide (IV). In order to confirm its structure, it was decarboxylated by heating and the product was derived to a picrate of yellow needles, m.p. 124°, which was found by mixed fusion to be identical with the picrate⁶⁾ of 2-picoline 1-oxide (V), thereby proving the structure of (IV). In

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1) Part III : This Bulletin, 3, 34(1955).

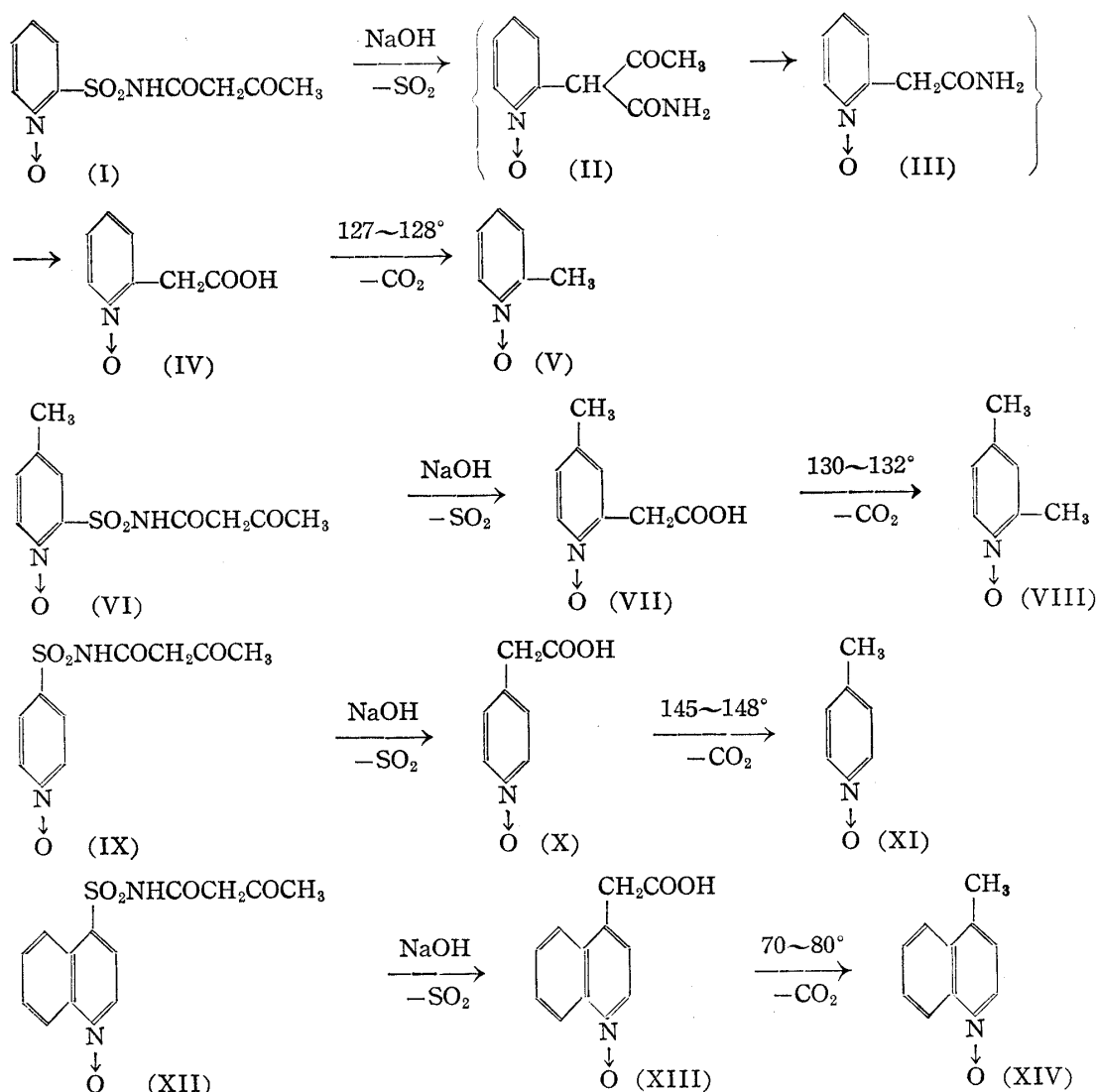
2) J. Pharm. Soc. Japan, 74, 593, 596(1954).

3) Phillips, Shapiro : J. Chem. Soc., 1942, 584.

4) T. Itai : J. Pharm. Soc. Japan, 69, 542(1949).

5) J. Roos : Ber., 21, 620(1888).

6) M. Ishikawa, Sai : J. Pharm. Soc. Japan, 63, 79(1943).



this reaction, (II) and (III) were not isolated and it was assumed that they underwent immediate hydrolyses to form (IV).

(VI) also undergoes rearrangement as (I) to form 4-methyl-2-pyridine-acetic acid 1-oxide (VII), m.p. $129\sim 130^\circ$ (decomp.), which was proved by deriving it to 2,4-lutidine 1-oxide (VIII). (IX) was similarly derived to 4-pyridine-acetic acid 1-oxide (X), m.p. $144\sim 145^\circ$ (decomp.), which was proved by deriving it to 4-picoline 1-oxide⁶⁾ (XI). (XII) similarly yielded 4-quinoline-acetic acid 1-oxide (XIII), m.p. 113° (decomp.), which easily underwent decarboxylation and formed lepidine 1-oxide⁷⁾ (XIV) by heating at 70° under a reduced pressure.

As another method for the synthesis, 2-(N-acetoacetyl)pyridinesulfonamide was reacted with hydrogen peroxide in glacial acetic acid to derive it to 1-oxide but deacetoacetylation took place to form 2-pyridinesulfonamide 1-oxide, and the objective could not be attained.

The writers extend their deep gratitude to Dr. Junzo Shinoda, the President of this Company, and to Mr. Isamu Nakano, Director to this Laboratory, for their unflinching encouragement. The writers are also grateful to Prof. E. Ochiai for the donation of 2,4-lutidine 1-oxide and to Messrs. Minoru Negishi and Katsuji Abe of this Factory for elemental analyses.

7) E. Ochiai, M. Ishikawa, Sai : J. Pharm. Soc. Japan, **65**, 16(1945).

Experimental

2-Pyridinesulfonamide—Cl₂ gas was bubbled for 1.5 hrs. through the mixture of 4 g. of 2-mercaptopyridine in 45 cc. of conc. HCl and 10 cc. of water, cooled to below 10°, and the clear yellow solution thereby formed was poured into 150 cc. of ice water. The white crystals that separated out were collected by filtration while chilling with ice and added to 80 cc. of conc. NH₃ water by which the crystals dissolved with generation of heat. After standing for 3 hrs., the solution was concentrated under a reduced pressure, and the crystals that separated out were collected by filtration. Yield, 3.1 g. (54.5%). Recrystallization from EtOH yielded colorless plates, m.p. 144~145°. *Anal.* Calcd. for C₅H₆O₂N₂S: C, 37.96; H, 3.82; N, 17.71. Found: C, 38.26; H, 4.21; N, 17.69.

2-Pyridinesulfonamide 1-Oxide—A solution of 0.79 g. of 2-pyridinesulfonamide dissolved in 1.5 cc. of 30% H₂O₂ and 2 cc. of glacial AcOH was warmed for 6 hrs. at 70~80°. The reaction mixture was concentrated under a reduced pressure, the crystals that separated out were collected by filtration, and recrystallized from a large amount of MeOH to colorless prisms, m.p. 228°. Yield, 0.6 g. (69%). *Anal.* Calcd. for C₅H₆O₃N₂S: C, 34.47; H, 3.47; N, 16.09. Found: C, 34.31; H, 3.63; N, 15.76.

2-(N-Acetoacetyl)pyridinesulfonamide 1-Oxide (I)—To a solution of 3.5 g. of 2-pyridinesulfonamide 1-oxide dissolved in a mixture of 0.8 g. of NaOH and 6 cc. of water, a solution of 2 g. of ketene dimer in 4 cc. of acetone was added dropwise under stirring, maintaining the temperature below 10°. The reaction mixture was allowed to stand over night, adjusted to pH 3.2 with 10% AcOH, and the crystals (0.25 g. of the starting material) that separated out were removed by filtration. The filtrate was acidified (pH 2.0) with 10% HCl, the crystals that separated out were collected, and recrystallized from MeOH to colorless plates, m.p. 152~153°(decomp.). Yield, 3.0 g. (58.2%). *Anal.* Calcd. for C₉H₁₀O₅N₂S: N, 10.84. Found: N, 10.88.

2-Mercapto-4-methylpyridine—A mixture of 8.6 g. of 2-bromo-4-methylpyridine and 3.8 g. of thiourea in 25 cc. of EtOH was refluxed for 1 hr., cooled, and 15 cc. of conc. NH₃ water was added to it. After allowing the mixture to stand for 24 hrs., it was concentrated under a reduced pressure, acidified with 10% AcOH, and extracted with 100 cc. of CHCl₃. After drying over Na₂SO₄, CHCl₃ was distilled off and the residual crystals were collected by filtration, washed with EtOH, and dried to 3 g. (48%) of pale yellow crystals. Recrystallization from benzene yielded pale yellow prisms, m.p. 179~180°. *Anal.* Calcd. for C₆H₇NS: C, 57.56; H, 5.64; N, 11.19. Found: C, 57.12; H, 5.76; N, 11.31.

4-Methyl-2-pyridinesulfonamide—Cl₂ gas was bubbled through the solution of 1.5 g. of 2-mercapto-4-methylpyridine dissolved in a mixture of 15 cc. of conc. HCl and 3 cc. of water, chilled to below 0°, and the content was poured on 20 g. of ice after 1.5 hrs. The crystals that separated out were collected rapidly by filtration, washed with ice-water, and placed in 20 cc. of conc. NH₃ water. This mixture was allowed to stand over night, the solution was concentrated under a reduced pressure, and the crystals that separated out were collected by filtration. Yield, 1.3 g. (63.1%). Recrystallization from EtOH yielded colorless needles, m.p. 163.5~164.5°. *Anal.* Calcd. for C₆H₈N₂S: C, 41.84; H, 4.68. Found: C, 41.32; H, 4.71.

4-Methyl-2-pyridinesulfonamide 1-Oxide—A mixture of 1.12 g. of 4-methyl-2-pyridinesulfonamide, 2.1 cc. of 30% H₂O₂, and 2.8 cc. of glacial AcOH was warmed on a water bath at 70~80° for 6 hrs. The reaction mixture was concentrated under a reduced pressure, the crystals that separated out were collected (0.98 g. or 74.4%) by filtration, and recrystallized from a large amount of MeOH to colorless needles, m.p. 222~223°. *Anal.* Calcd. for C₆H₈O₃N₂S: C, 38.29; H, 4.28; N, 14.88. Found: C, 38.22; H, 4.39; N, 14.83.

4-Methyl-2-(N-acetoacetyl)pyridinesulfonamide 1-Oxide (VI)—To a solution of 750 mg. of 4-methyl-2-pyridinesulfonamide 1-oxide dissolved in a mixture of 160 mg. of NaOH in 1.5 cc. of water, solution of 500 mg. of ketene dimer in 1 cc. of acetone was added dropwise under stirring, while chilling with ice, and the mixture was allowed to stand overnight. The crystals that separated out were removed by filtration, the filtrate was adjusted to pH 2.0 with 10% HCl, and the crystals that separated out were collected by filtration. Yield, 810 mg. (74.4%). Recrystallization from EtOH yielded colorless needles, m.p. 153~154°. *Anal.* Calcd. for C₁₀H₁₂O₅N₂S: C, 44.11; H, 4.44. Found: C, 43.84; H, 4.49.

4-Pyridinesulfonamide 1-Oxide—Cl₂ gas was bubbled for 1.5 hrs. through the solution of 3 g. of 4-mercaptopyridine 1-oxide in a mixture of 30 cc. of conc. HCl and 8 cc. of water, chilled to -5° to 0°, and the solution was poured on 15 g. of ice, and this was poured into 100 cc. of conc. NH₃ water. After allowing the mixture to stand over night, the solution was evaporated to dryness under a reduced pressure, the residue was extracted with 200 cc. of acetone, and the extract was evaporated to dryness. The residue was recrystallized from EtOH to 2 g. (48.8%) of colorless prisms, m.p. 228°(decomp.). *Anal.* Calcd. for C₅H₆O₃N₂S: C, 34.48; H, 3.45. Found: C, 34.64; H, 3.29.

4-(N-acetoacetyl)pyridinesulfonamide 1-Oxide (IX)—To a solution of 1.8 g. of 4-pyridinesulfonamide 1-oxide dissolved in a mixture of 0.4 g. of NaOH and 3 cc. of water, a solution of 1 g. of

ketene dimer in 2 cc. of acetone was added dropwise while maintaining the temperature at below 10°, and the mixture was allowed to stand over night. The crystals were removed by filtration, the filtrate was adjusted to pH 2.0 with 10% HCl, the crystals that separated out were collected by filtration, and recrystallized from MeOH to 1.7 g. (65.9%) of colorless rhombs, m.p. 183~184°(decomp.). *Anal.* Calcd. for $C_9H_{10}O_3N_2S$: N, 10.84. Found: N, 10.53.

4-Quinolinesulfonamide 1-Oxide—Cl₂ gas was bubbled for 2 hrs. through a solution of 2.5 g. of 4-mercaptoquinoline 1-oxide dissolved in a mixture of 20 cc. of conc. HCl and 4 cc. of water, maintained at -5° to 0°, and the yellow crystals that separated out were removed by filtration. The filtrate was poured on 15 g. of chipped ice, the crystals that separated out were collected and added to 50 cc. of conc. NH₃ water. After allowing the mixture to stand over night, the solution was concentrated under a reduced pressure, the crystals were collected by filtration, and recrystallized from a large amount of MeOH to 1.1 g. (35%) of colorless needles, m.p. 228°(decomp.). *Anal.* Calcd. for $C_9H_8O_3N_2S$: C, 48.20; H, 3.59; N, 12.49. Found: C, 48.38; H, 3.42; N, 12.41.

4-(N-Acetoacetyl)quinolinesulfonamide 1-Oxide (XII)—To a solution of 1.1 g. of 4-quinolinesulfonamide 1-oxide and 0.2 g. of NaOH dissolved in 2.5 cc. of water, a solution of 0.5 g. of ketene dimer in 1 cc. of acetone was added dropwise, at below 10°, the mixture was allowed to stand over night, and adjusted to pH 3.6 with 10% AcOH. The crystals (0.4 g. of the starting material) were removed by filtration, the filtrate was adjusted to pH 2.0, and the crystals that separated out were collected by filtration and recrystallized from EtOH-acetone mixture to 1.1 g. (71.5%) of colorless needles, m.p. 172~173°(decomp.). *Anal.* Calcd. for $C_{13}H_{12}O_5N_2S$: N, 9.08. Found: N, 8.59.

Rearrangement Reaction of 2-(N-Acetoacetyl)pyridinesulfonamide 1-Oxide: Formation of (IV)—A mixture of 520 mg. of the sample in 4 cc. of 10% NaOH was heated on a water bath (90~95°) for 30 mins., acidified with 10% HCl, by which white crystals separated out with liberation of SO₂. The crystals were collected by filtration, the filtrate was evaporated to dryness under a reduced pressure, 2 cc. of water was added to the residue, and the crystals were collected by filtration. The two lots of crystals were combined and recrystallized from MeOH to 190 mg. (62.2%) of (IV), m.p. 125~126°(decomp.). *Anal.* Calcd. for $C_7H_7O_3N$: N, 9.15. Found: N, 9.37.

Thirty mg. of this substance was placed in a small test tube and heated in an oil bath of 127~128°, by which the crystals underwent decomposition with effervescence to form a clear, pale yellow, viscous liquid. Its picrate was recrystallized from MeOH to yellow needles, m.p. 124°, undepressed on admixture with the picrate of 2-picoline 1-oxide.

Rearrangement Reaction of 4-Methyl-2-(N-acetoacetyl)pyridinesulfonamide 1-Oxide (VI): Formation of (VII)—A solution of 540 mg. of the sample in 4 cc. of 10% NaOH was heated on a water bath (90~95°) for 1 hr., adjusted to pH 2.0 with 10% HCl, and evaporated under a reduced pressure. The crystals (200 mg. or 60%) that separated out were collected by filtration and recrystallized from MeOH to colorless plates (VII), m.p. 129~130°(decomp.). *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.47; H, 5.42; N, 8.38. Found: C, 57.27; H, 4.71; N, 8.82.

Twenty mg. of this substance was placed in a small test tube and heated in an oil bath of 130~132° by which it underwent decomposition with effervescence to form a yellow oil. Recrystallization of its picrate from acetone yielded crystals of m.p. 139~140°, undepressed on admixture with the picrate of 2,4-lutidine 1-oxide.

Rearrangement Reaction of 4-(N-Acetoacetyl)pyridinesulfonamide 1-Oxide: Formation of (X)—A mixture of 520 mg. of the sample and 4 cc. of 10% NaOH solution was heated on a water bath (90~95°) for 30 mins., adjusted to pH 2.2 with 10% HCl, and evaporated to dryness under a reduced pressure. The residue was extracted with dehyd. EtOH and 220 mg. (71.9%) of the extract thereby obtained was recrystallized from EtOH to white needles (X), m.p. 144~145°(decomp.). *Anal.* Calcd. for $C_7H_7O_3N$: C, 54.91; H, 4.61; N, 9.15. Found: C, 55.07; H, 4.47; N, 8.88.

Thirty mg. of this substance was placed in a small test tube and heated in an oil bath at 145~148°, and a pale yellow viscous liquid was obtained. Recrystallization of its picrate from MeOH yielded yellow needles, m.p. 153.5~154.5°, which showed no depression on admixture with the picrate of 4-picoline 1-oxide.

Rearrangement Reaction of 4-(N-Acetoacetyl)quinolinesulfonamide 1-Oxide (XII): Formation of (XIII)—A mixture of 310 mg. of the sample in 2 cc. of 10% NaOH solution was heated on a water bath for 1.5 hrs. at 90~95°, and its acidification with 10% HCl separated some white crystals. The crystals were collected, dissolved in alkali, and again acidified to effect purification. White crystals (XIII), m.p. 113°(decomp.). *Anal.* Calcd. for $C_{11}H_9O_3N$: C, 65.02; H, 4.47; N, 6.89. Found: C, 64.58; H, 5.08; N, 7.17.

This substance, when heated at 70~80° under a reduced pressure, underwent decomposition and recrystallization of the product from ether furnished colorless needles, m.p. 67° (m.p. 120° when dried), undepressed on admixture with lepidine 1-oxide.

Summary

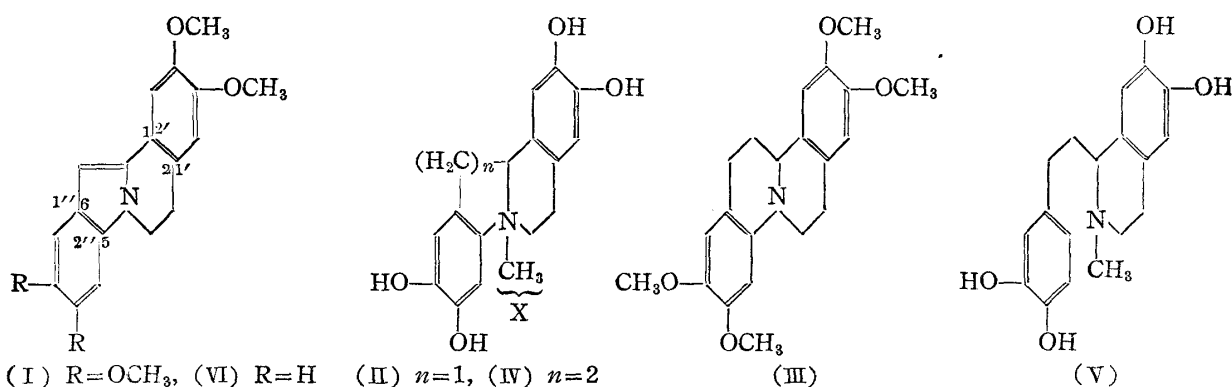
Heating of 1-oxides of 2-(N-acetoacetyl)pyridinesulfonamide, 4-methyl-2-(N-acetoacetyl)pyridinesulfonamide, 4-(N-acetoacetyl)pyridinesulfonamide, and 4-(N-acetoacetyl)-quinolinesulfonamide each in 10% sodium hydroxide at 90~95° causes rearrangement reaction with liberation of sulfur dioxide to form respectively, 2-pyridineacetic acid, 1-oxides of 4-methyl-2-pyridineacetic acid, 4-pyridineacetic acid, and 4-quinolineacetic acid. These substances were confirmed by their respective decarboxylation and derivation to 2-picoline 1-oxide, 2,4-lutidine 1-oxide, 4-picoline 1-oxide, and lepidine 1-oxide.

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11. Shigehiko Sugasawa and Kitaro Mizukami : Studies on the Synthesis of Dibenzoindolizine Derivatives. V. Synthesis of 4',5' : 4'',5''-Tetramethoxy-3,4-dihydro-(2',1' : 1,2 ; 2'',1'' : 5,6-dibenzoindolizine).**

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This paper describes the synthesis of dibenzoindolizine derivative (I) mentioned in the title, related to dehydrolaudanoline salt (II), furnishing the synthetic support for the proposed structure (II) of the latter compound. This compound was first placed on record by Robinson and Sugasawa¹⁾ as an unexpected dehydrogenation product of laudanoline salt, to which they ascribed the formula (II) chiefly based upon the experimental data in Hofmann and Emde degradations. Indirect synthetic support was, however, offered, when Sugasawa and Kakemi²⁾ succeeded in synthesizing the homo compound (III) related to (II), which was proved to be identical with the compound derived from dehydrohomolaudanoline salt (IV), obtained by applying Robinson and Sugasawa's dehydrogenation method upon homolaudanoline (V) salt.³⁾



It may be considered rather unusual that the (II)-type alkaloid, the *in vitro*-formation of which proceeds with such an ease, has not yet been located in the vegetable kingdom. Though Folkers⁴⁾ once supposed this kind of skeleton for some of the erythrina alkaloids,

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** Part IV : Sugasawa, Kodama : Proc. Imp. Acad. (Tokyo), **18**, 565(1942); J. Pharm. Soc. Japan, **63**, 54(1943).

1) J. Chem. Soc., **1932**, 789; cf. also Schöpf, Thielfelder : Ann., **497**, 22(1932); Harley-Mason : J. Chem. Soc., **1953**, 1465.

2) Ber., **71**, 1860(1938).

3) Sugasawa, Yoshikawa : J. Chem. Soc., **1933**, 1583.

4) J. Am. Chem. Soc., **73**, 589(1951).