Summary

A new colorimetric determination of cholesterol has been established, using anhydrous aluminum chloride and anisaldehyde as reagents. The limit and scope of the reaction on steroid was investigated, and it is concluded that a steroid having a double bond not conjugated to a carbonyl group, or having a hydroxyl group easily dehydrated gives a positive result. Availability of the reagents and difference from other known color reactions are also discussed.

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83. Takeo Naito, Renzo Dohmori, and Tatuo Kotake: Rearrangement of Sulfonamide Derivatives. V.[*1] Syntheses of Methyl α-Phenyl-2- and 4-piperidineacetate.

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In the preceding paper of this series, it was shown that the rearrangement reaction of N-acetoacetyl-2- or 4-pyridinesulfonamide 1-oxide in alkaline solution formed 2- or 4-pyridineacetic acid 1-oxide in a good yield. And these results suggested that the reaction of N-phenylacetyl-2- or 4-pyridinesulfonamide 1-oxide in alkaline solution will proceed exactly the same as in the case of N-acetoacetyl derivatives.

In the present paper, an application of this rearrangement was extended to the preparation of the medicine, methyl α-phenyl-2-piperidineacetate[*3] and its homologues.

N-Phenylacetyl-2-pyridinesulfonamide 1-oxide (Ⅱ), m.p. 190° (decomp.), was synthesized by the condensation of 2-pyridinesulfonamide 1-oxide (Ⅰ) with phenylacetyl chloride. Application of the same synthetic procedure to 4-pyridinesulfonamide 1-oxide (Ⅷ) gave N-phenylacetyl-4-pyridinesulfonamide 1-oxide (Ⅸ), m.p. 198~199° (decomp.).

The rearrangement reaction was applied to these obtained compounds.

Ⅱ evolved ammonia in 10% sodium hydroxide at 90~95°, and a resulting solution generated a strong odor of sulfur dioxide when it was acidified with hydrochloric acid. It suggested that the rearrangement reaction occurred. The reaction mixture gave colorless crystals, m.p. 102° (decomp.), whose elemental analytical values corresponded to those of α-phenyl-2-pyridineacetic acid 1-oxide (Ⅳ). In order to confirm its structure, it was decarboxylated by heating to produce a colorless needle, m.p. 101°, which was converted into a picrate, m.p. 121~122°. The elemental analytical values of these compounds corresponded to those of 2-benzylpyridine 1-oxide (Ⅴ) and its picrate respectively. In this rearrangement, Ⅱ liberated sulfur dioxide to form Ⅲ which is hydrolized to Ⅳ immediately, as reported in the preceding paper.[*1] Ⅳ gave the methyl ester (Ⅵa), m.p. 111~113° and ethyl ester (Ⅵb), m.p. 50~60°, by treatment with alcoholic hydrochloride.

N-Phenylacetyl-4-pyridinesulfonamide 1-oxide (Ⅸ) underwent rearrangement in alkaline solution to form α-phenyl-4-pyridineacetic acid 1-oxide (Ⅺ), m.p. 98~99° (decomp.),

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*3 The trade name of this compound: Methylphenidate Hydrochloride or Ritaline.

which was converted into 4-benzylpyridine 1-oxide (XII) in boiling ethanol. Methyl ester (XIII) of XI was oily which was crystallized as picrate.

Hydrogenation of these three esters of α-phenyl-pyridineacetic acid 1-oxide over Adams' platinum-catalyst gave the respective products, methyl α-phenyl-2-piperidineacetate hydrochloride (VIIa), m.p. 211° (decomp.), methyl α-phenyl-4-piperidineacetate hydrochloride (XIV), m.p. 214° (decomp.), and ethyl α-phenyl-2-piperidineacetate hydrochloride (VIIb), m.p. 174~175°.

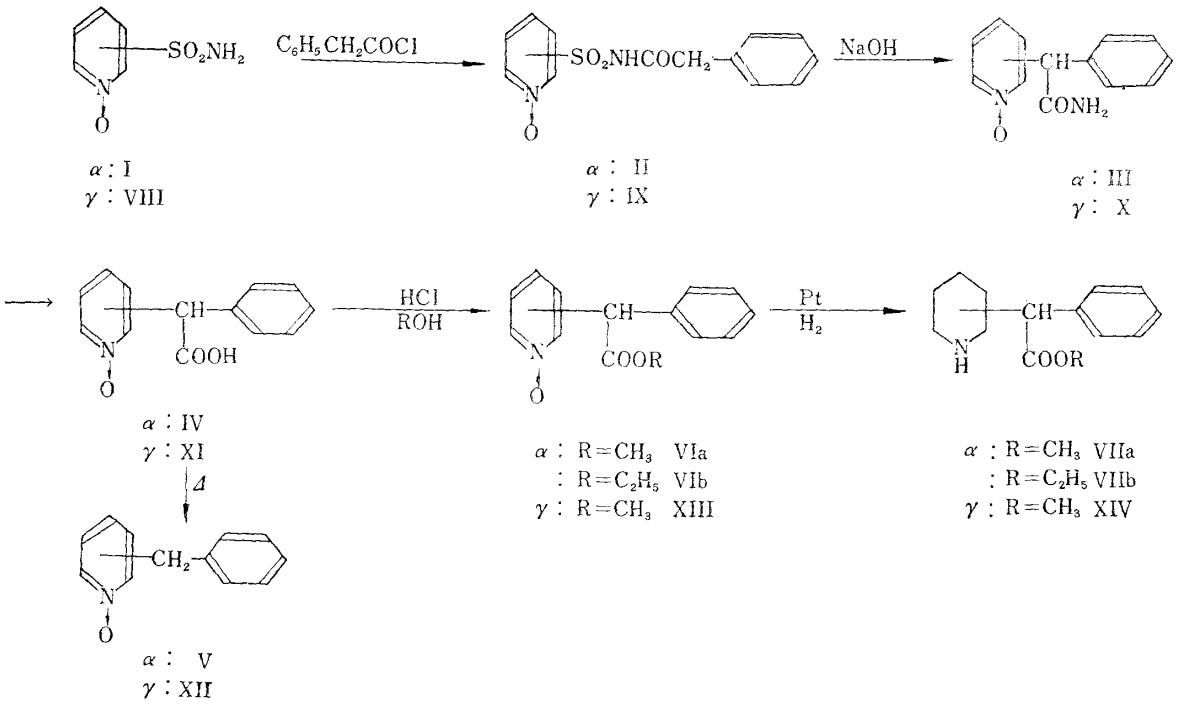

Chart 1.

Experimental*1

N-Phenylacetyl-2-pyridinesulfonamide 1-Oxide (II)——To a solution of 2-pyridinesulfonamide 1-oxide (10 g.) in 10% Na_2CO_3 (200 ml.) was added dropwise phenylacetyl chloride (24 g.) under stirring at 0~2°. The reaction mixture was allowed to stand for 1 hr. at the same temperature and for another 2 hr. at a room temperature. Some insoluble materials were removed by filtration and the filtrate was acidified with HCl. The resulting precipitate was collected by suction and washed with benzene. Recrystallization from MeOH afforded colorless prisms, m.p. 190° (decomp.). Yield, 10.8 g. (64.3%). *Anal.* Calcd. for $C_{13}H_{12}O_4N_2S$: C, 53.41; H, 4.14; N, 9.59. Found : C, 53.61; H, 4.31; N, 9.97.

Rearrangement Reaction of N-Phenylacetyl-2-pyridinesulfonamide 1-Oxide (II) : Formation of IV——A solution of II (1.75 g.) in 10% NaOH (9 ml.) was heated on a steam bath for 1.5 hr. By acidification of the reaction mixture with 10% HCl, colorless crystals, m.p. 102° (decomp.), were collected by filltration and rinsed with Et_2O. Yield, 1.1 g. (80.1%). *Anal.* Calcd. for $C_{12}H_{11}O_3N$: C, 67.78; H, 4.84; N, 6.11. Found : C, 68.11; H, 4.62; N, 6.45. IR ν_{max}^{KBr} cm^{-1} : 1710 (C=O in COOH).

2-Benzylpyridine 1-Oxide (V)——IV (200 mg.) was dissolved in EtOH (5 ml.) and heated on a steam bath (70~80°) for 1 hr. The solvent was evaporated, and the reaction mixture was allowed to stand for 2 days in a vacuum desiccator and crystallized. Colorless crystals, m.p. 101°. Yield, 150 mg. (93.4%). *Anal.* Calcd. for $C_{12}H_{11}ON$: C, 77.80; H, 5.99; N, 7.56. Found : C, 77.77; H, 6.19; N, 7.31. Picrate : pale yellow needles, m.p. 121~122°. *Anal.* Calcd. for $C_{18}H_{14}O_8N_4$: C, 52.19; H, 3.41; N, 13.53. Found : C, 52.27; H, 3.21; N, 13.49.

Methyl α-Phenyl-2-pyridineacetate 1-Oxide (VIa) and Ethyl α-Phenyl-2-pyridineacetate 1-Oxide (VIb)——HCl gas was bubbled through the solution of IV (2.6 g.) in MeOH (230 ml.), chilled to below 0°, and the clear yellow solution thereby formed was allowed to stand for 40 hr. at a room temperature.

*1 All melting points are uncorrected.

The reaction mixture was evaporated under a reduced pressure. The residue was treated with H_2O, neutralized with 10% Na_2CO_3, and extracted with $CHCl_3$ (40 ml.). The $CHCl_3$ extract was dried with anhyd. Na_2SO_4, the solvent was distilled off to give pale yellow crystals. The crystals washed with a small volume of Et_2O and recrystallized from Et_2O to form colorless crystals, m.p. 111~113°. Yield, 2.0 g. (72.4%). *Anal.* Calcd. for $C_{14}H_{13}O_3N$: C, 69.16; H, 5.39; N, 5.76. Found : C, 68.81; H, 5.22; N, 5.77.

Ethyl ester (Ⅵb), m.p. 50~60°, was also obtained from Ⅳ (2.6 g.) by the same procedure as described above. Yield, 1.9 g. (68.5%).

Methyl α-Phenyl-2-piperidineacetate Hydrochloride (VIIa) and Ethyl α-Phenyl-2-piperidineacetate Hydrochloride (VIIb)——A mixture of Ⅵa (1.47 g.), PtO_2 (370 mg.), 10% HCl (10 ml.) and EtOH (60 ml.) was subjected to hydrogenation under atmospheric pressure at a room temperature. Hydrogenation was stopped after 4 molar equivalents of H_2 had been absorbed (about 14 hr.). After removal of the catalyst and the solvent, the crystalline residue was collected and washed with Me_2CO. Recrystallization of this compound from MeOH+AcOEt afforded a colorless prism, m.p. 211° (decomp.), which was identified by admixture and by the IR spectra with an authentic sample prepared in usual way.[1] Yield, 1.23 g. (75.6%).

Ethyl ester (Ⅵb) was reduced by the similar procedure described above to given Ⅶb, needles (from Et_2O+Me_2CO), m.p. 174~175°. Yield, 68.3%. *Anal.* Calcd. for $C_{15}H_{21}O_2N \cdot HCl$: C, 63.49; H, 7.81; N, 4.94. Found : C, 63.20; H, 7.26; N, 4.59.

N-Phenylacetyl-4-pyridinesulfonamide 1-Oxide (IX)——Phenylacetyl chloride (8 g.) was added to a mixture of 4-pyridinesulfonamide 1-oxide (4 g.) in 20% Na_2CO_3 (60 ml.) and Me_2CO (60 ml.) under stirring at 0~5°. The reaction mixture was allowed to stand for 1 hr. at a room temperature and filtered. The filtrate was acidified with HCl, concentrated to a small volume under a reduced pressure and allowed to stand in a refrigerator overnight. The crystals were washed with Et_2O and recrystallized from MeOH to colorless prisms, m.p. 198~199° (decomp.). Yield, 3.9 g. (58.1%). *Anal.* Calcd. for $C_{13}H_{12}O_4N_2S$: C, 53.41; H, 4.14; N, 9.59. Found : C, 53.28; H, 4.45; N, 9.18.

Rearrangement Reaction of N-Phenylacetyl-4-pyridinesulfonamide 1-Oxide (IX) : Formation of 4-Pyridineacetic Acid 1-Oxide (XI)——A solution of Ⅸ (3.13 g.) in 10% NaOH (15.9 ml.) was heated at 90° for 1.5 hr. and acidified with HCl. The resulting precipitate, m.p. 98~99° (decomp.) was collected. Yield, 2 g. (81.7%). *Anal.* Calcd. for $C_{13}H_{11}O_3N$: C, 68.11; H, 4.84; N, 6.11. Found : C, 67.70; H, 4.78; N, 6.21. IR ν_{max}^{KBr} cm^{-1} : 1702 (C=O in COOH).

4-Benzylpyridine 1-Oxide (XII)——A solution of Ⅺ (200 mg.) in EtOH (5 ml.) was warmed on a steam bath for 1 hr. After removal of the solvent, Ⅻ was appeared as an oily material in 93.4% yield (150 mg.), which was converted into a picrate. Picrate : pale yellow needles, m.p. 102~103°. *Anal.* Calcd. for $C_{18}H_{14}O_8N_4$: C, 52.19; H, 3.41; N, 13.53. Found : C, 52.00; H, 3.94; N, 13.44.

Methyl α-Phenyl-4-pyridineacetate 1-Oxide (XIII)——HCl gas bubbled through the solution of Ⅺ (3.5 g.) in MeOH (300 mg.) at 0° and the clear yellow solution was allowed to stand for 40 hr. at a room temperature. The reaction mixture was evaporated under a reduced pressure. The residue was treated with H_2O, neutralized with 10% Na_2CO_3, and extracted with $CHCl_3$ (60 ml.). After drying with anhyd. Na_2SO_4, the $CHCl_3$ solution was distilled off to give a yellowish oil in 80.0% yield (3 g.), which was converted into a picrate. Picrate : yellow needles (from EtOH), m.p. 133~134°. *Anal.* Calcd. for $C_{20}H_{16}O_{10}N_4$: C, 50.86; H, 3.41. Found : C, 50.66; H, 3.76.

Methyl α-Phenyl-4-piperidineacetate Hydrochloride (XIV)——A mixture of crude XIII (1.4 g.), PtO_2 (70 mg.), 10% HCl (10 ml.) and EtOH (40 ml.) was submitted to reduction at ordinary temperature and pressure. The reaction stopped after absorption of ca. 4 moles of H_2. After removal of the catalyst and the solvent, the crystalline residue was collected and washed with Me_2CO. Recrystallization of this material from MeOH+AcOEt gave colorless prisms, m.p. 214° (decomp.). Yield, 0.7 g. (45.1%). *Anal.* Calcd. for $C_{14}H_{19}O_2N \cdot HCl$: C, 62.33; H, 7.47; N, 5.19. Found : C, 62.16; H, 7.44; N, 4.61.

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Summary

Heating of N-phenylacetyl-2- and 4-pyridinesulfonamide 1-oxides in 10% sodium hydroxide at 90~95° caused rearrangement reaction to form α-phenyl-2- and 4-pyridineacetic acid 1-oxides respectively. Their respective esterification and catalytic reduction with platinum-catalyst gave the hydrochloride of methyl 2- and 4-piperidineacetate and ethyl 2-piperidineacetate.

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1) L. Panizzon : Helv. Chim. Acta, **27**, 1748 (1944).