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27. Seiki Kasuga*1 and Tanezo Taguchi: Heteroalicyclic Aminoalkanol. I. Syntheses of DL-2-Piperidinemethanol and *meso-cis*-2,6-Piperidinedimethanol and Reactions of Intermediates.*2

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Stereochemistry of acyclic and alicyclic aminoalkanols which has been extensively investigated was attempted to be expanded into heteroalicyclic field. The attempt started from examining reactions of 2-piperidinemethanols which were synthesized through a few steps from 2-picoline (I) and 2,6-lutidine (II). This report deals with synthetic steps of the compounds and additional reactions of intermediates. Boekelheide, *et al.*[1] has reported that thermal treatment with acetic anhydride converted I N-oxide to 2-pyridinemethanol acetate (III) and II N-oxide to 6-methyl-2-pyridinemethanol acetate (IV). IV was, then, converted to 2,6-pyridinedimethanol diacetate (VI) on treatment with hot acetic anhydride after derivation to IV N-oxide (V).[1]

The procedure[1] was applied here to prepare 2-pyridinemethanol (XXX) and 2,6-pyridinedimethanol (VIII) which were precursors of the tittle compounds. More recently, Kato, *et al.*[2] found the formation of 6-methylpicolinaldehyde diacetate (VII) and 3-hydroxy-6-methyl-2-pyridinemethanol in addition to the known product (VI) in acetolysis of IV N-oxide. Kaneko, *et al.*[3] discussed the reaction mechanism. These reports prompted us to treat analogously 2-bromomethyl-6-methylpyridine 1-oxide (X), 6-methyl-2-pyridinemethanethiol 1-oxide (XI) and 2-ethylthiomethyl-6-methylpyridine 1-oxide (XII).

After the treatment, the following results were obtained*4: The reaction mixture from X was distilled and subsequently treated with 47% aq. hydrogen bromide to give 2,6-bis(bromomethyl)pyridine (XV), yield 39.6%, and 6-methylpicolinaldehyde (IX), yield 16.2%. The formation of products, XV and IX, provided support for the reaction passing through 6-bromomethyl-2-pyridinemethanol acetate (XIII) and α-bromo-6-methyl-2-pyridinemethanol acetate (XIV). See Chart 1. In the case of XI, the reaction was carried out in the stream of nitrogen and gave a tarry substance and 6-methyl-2-pyridinemethanethiol acetate (XVI), yield 21%, which was identical with an authentic sample prepared by the action of sodium thiolacetate on 2-bromomethyl-6-methylpyridine.[4]

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*2 T. Taguchi: Studies in Stereochemistry. XXXIII. Part XXXII: J. Org. Chem., **29**, 1104 (1964).

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*4 In acetolyses tried here, other products would be possibly formed, but precise detections of them were omitted.

1) V. Boekelheide, W. J. Linn: J. Am. Chem. Soc., **76**, 1286 (1954).
2) T. Kato, T. Kitagawa, T. Shibata, K. Nakai: Yakugaku Zasshi, **82**, 1647 (1962).
3) C. Kaneko, S. Yamada, I. Yokoe: The Report of Research Institute of Dental Materials (Tokyo Medical and Dental University), **2**, 475 (1963).
4) W. Baker, K. M. Buggle, J. F. W. McOmie, P. A. M. Watkins: J. Chem. Soc., **1958**, 3594.

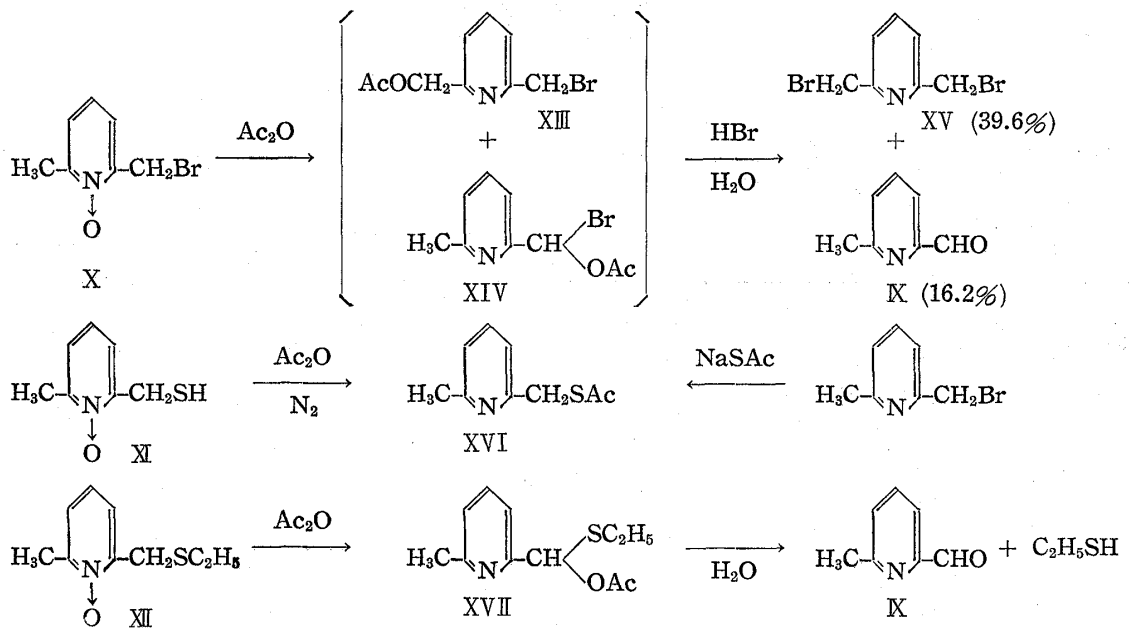


Chart 1.

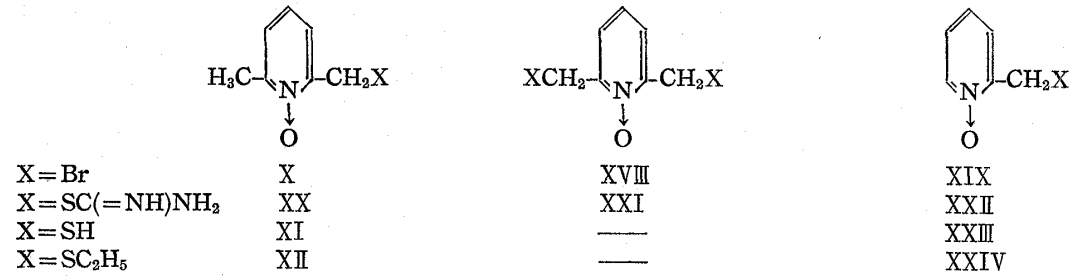


Chart 2.

Acetolysis of XII gave rise to α-ethylthio-6-methyl-2-pyridinemethanol acetate (XVII) in a good yield, 84.2%, which was characterized by the finding that it was hydrolized to 6-methylpicolinaldehyde (IX) and ethanethiol.

The starting materials, X, XI, and XII, and their analogues were prepared in the following ways. The bromomethyl derivatives of 1-oxido-pyridine, X, XVIII, and XIX,[5] as shown in Chart 2, were derived from the corresponding acetoxymethyl derivatives on treatment with hydrobromic acid. XI was yielded by action of hydrogen sodium sulfide on X and also by hydrolysis of 2-(6-methyl-2-pyridylmethyl)-2-thiopseudourea N-oxide (XX) which was prepared by reaction of thiourea with X. The analogues of XX, 2,2′-(1,6-pyridinediyldimethyl)bis[2-thiopseudourea] N-oxide(XXI) and 2-(2-pyridylmethyl)-2-thiopseudourea N-oxide (XXII), were prepared analogously to XX. XXII was converted to 2-pyridinemethanethiol 1-oxide (XIII) by hydrolysis. XI and XXIII were oxidized to the corresponding disulfides which were identical with compounds prepared by action of sodium disulfide on X and XIX respectively. In passing, the corresponding sulfides also were prepared (See Experimental). XII and 2-ethylthiomethylpyridine 1-oxide (XXIV) were yielded by action of sodium ethanethiolate on X and XIX respectively.[6]

5) M. Hamana, B. Umezawa, Y. Goto, K. Noda : This Bulletin, 8, 692 (1960).
6) All sulfur derivatives prepared here lack the antifungal activity, while 2-pyridinethiol 1-oxide possesses it.[7,8]
7) A. K. Sijpesteijn, M. J. Janssen, H. M. Dekhuyzen : Nature, **180**, 505 (1957); A. K. Sijpesteijn, M. J. Janssen : *Ibid.*, **182**, 1313 (1958).
8) J. Dekker, O. M. Van Andel : Nature, **181**, 1017 (1958).

In the next place, X and XIX were submitted to treatment with aq. sodium hydroxide at room temperature. Surprisingly, the reactions resulted in the formation of 2,2′-oxydimethyl-6,6′-dimethyldipyridine 1,1′-dioxide (XXV) and 2,2′-oxydimethyldipyridine 1,1′-dioxide (XXVI) respectively in good yields, 82.3% and 88.3%. The structures of the products were supported by molecular weight determinations and infrared spectra, λ_{max}^{Nujol} μ : 8.73, 8.10, due to ether and N-oxide linkages. Moreover, they were established by mixture melting point determinations with authentic samples prepared by N-oxidation of 2,2′-oxydimethyl-6,6′-dimethyldipyridine (XXVII) and 2,2′-oxydimethyldipyridine (XXVIII) which were obtained by dehydration of 6-methylpyridinemethanol (XXIX) and 2-pyridinemethanol (XXX) with conc. sulfuric acid. Analogously, the alkaline treatment of 6-methyl-2-bromomethylpyridine (XXXI) and 2-bromomethylpyridine (XXXII) gave XXVII and XXVIII respectively, which were also yielded from XXV and XXVI by deoxidation with phosphorus trichloride. Treatment with hydrobromic acid converted XXV and XXVI to X and XIX respectively. See Chart 3.

The formation of the ether linkage, seems possible to come from dehydrobromination between the bromomethyl group and the hydroxymethyl group which is partially formed during the reaction by the alkaline treatment of the bromomethyl group.

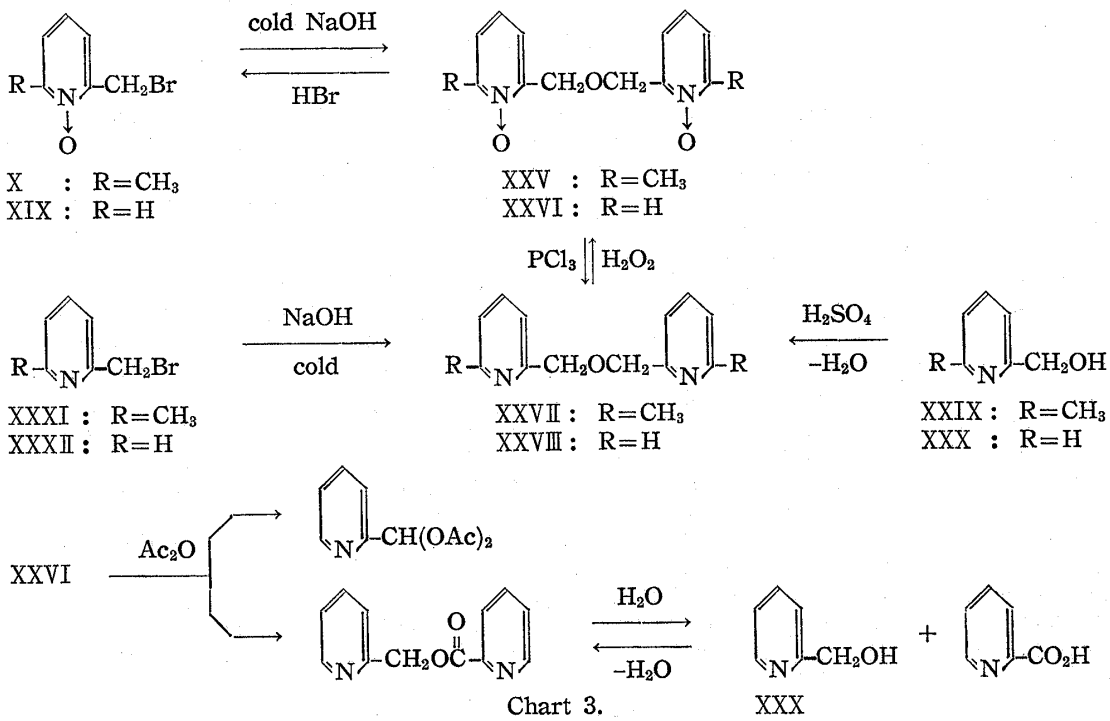


Chart 3.

But the possibility is excluded because the alkaline treatment of an equimolecular mixture of XIX and 2-pyridinemethanol 1-oxide (XXXIII) gave the ether derivative (XXVI) in yield inferior to 50% and XXXIII remained unchanged. Thus the formation mechanism has still been obscure.

XXVI was treated with hot acetic anhydride to give picolinaldehyde diacetate, yield 15.5%, and 2-pyridylmethyl picolinate, yield 46.6%,

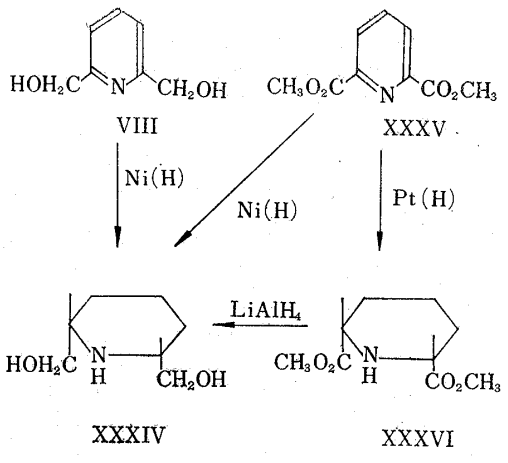
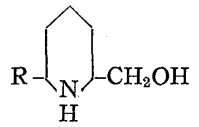


Chart 4.

which was identical with the product yielded by esterification of 2-pyridinecarboxylic acid with 2-pyridinemethanol (XXX).

Synthesis of DL-2-piperidinemethanol (XXXIII) has been done by a couple of authors.[9~11] In the present study, 2-pyridinemethanol (XXX) was hydrogenated to XXXIII over Raney nickel in high yield (90.7%). An isomer of 2,6-piperidinedimethanols (XXXIV) has been synthesized from alkyl 2,6-pyridinedicarboxylate by hydrogenation of the nucleus over platinum-catalyst followed by reduction of the ester group with lithium aluminum hydride.[12] But the configuration of the isomer (XXXIV) has still been unknown. Hydrogenation of VIII over Raney nickel was successfully tried to yield the same isomer (XXXIV). The configuration of XXXIV was assigned as *cis* because it was identical with the product yielded by reduction of *meso-cis*-methyl-2,6-piperidinedicarboxylate (XXXVI)[13] with lithium aluminum hydride. Hydrogenation over Raney nickel converted methyl 2,6-pyridinedicarboxylate (XXXV) directly to XXXIV.



R=H : XXXIII
R=CH_2OH : XXXIV

Experimental*5

2-Bromomethyl-6-methylpyridine 1-Oxide (X)——A solution of V (20 g.) in 48% aq. HBr (100 ml.) was refluxed for 4 hr., concentrated under reduced pressure and a small volume of ethanol added to cause the precipitation of crystals. Recrystallization from ethanol gave colorless granules of m.p. 172~173°, yield 27.1 g. (86%). An aqueous solution saturated with the product was neutralized with sodium bicarbonate, extracted with chloroform, dried over anhyd. sodium sulfate and evaporated to dryness. The residue was recrystallized from acetone to give colorless pillars of m.p. 123~124°. *Anal.* Calcd. for C_7H_8NOBr (X) : C, 41.61; H, 3.99; N, 6.93. Found : C, 41.77; H, 4.11, N, 7.10.

2,6-Bis(bromomethyl)pyridine 1-Oxide (XVIII)——Ten grams of 2,6-pyridinedimethanol diacetate 1-oxide[1,4] was treated just like the foregoing item to give a crude product of XVIII. Recrystallization from methanol furnished colorless granules of m.p. 153~155°, yield 10.5 g. (89%). *Anal.* Calcd. for $C_7H_7ONBr_2$ (XVIII) : C, 29.92; H, 2.51; N, 4.99. Found : C, 30.09; H, 2.75; N. 5.10.

2-(2-Pyridylmethyl)-2-thiopseudourea N-Oxide (XXII) Hydrobromide——The free base liberated from 5 g. of 2-bromomethylpyridine 1-oxide (XIX)[5] on alkaline treatment was dissolved in 100 ml. of ethanol and 1.2 g. of thiourea was added to the solution. The solution was heated on a water bath for 2.5 hr. and cooled. The precipitate was filtered and recrystallized from methanol to give colorless pillars of m.p. 184~185° (decomp.), yield 3.5 g. (52.5%). *Anal.* Calcd. for $C_7H_9ON_3S \cdot HBr$ (XXII·HBr); C, 31.82; H, 3.79; N, 15.91. Found : C, 32.13; H, 3.84; N, 15.70.
Picrate : recrystallized from water, m.p. 198° (decomp.).

2-(6-Methyl-2-pyridylmethyl)-2-thiopseudourea N-Oxide (XX) Hydrobromide——X was treated just like the preparation of XXII·HBr to give a crude product of XX·HBr. Recrystallization from ethanol afforded colorless pillars of m.p. 191~192°, yield 88.7%. *Anal.* Calcd. for $C_8H_{11}ON_3S \cdot HBr$: C, 34.54; H, 4.35; N, 15.11. Found : C, 34.58; H, 4.38; N, 14.83.

2,2'-(1,6-Pyridinediyldimethyl)bis[2-thiopseudourea] N-Oxide (XXI) Dihydrobromide——The preparation method of XXII·HBr was applied for yielding of crude XXI·2HBr from XVIII. Recrystallization from ethanol gave colorless granules of m.p. 203~205° (decomp.), yield 65%. *Anal.* Calcd. for $C_9H_{13}ON_5S_2 \cdot 2HBr$: C, 24.95; H, 3.49; N, 16.16. Found : C, 24.88; H, 3.75; N, 16.16.

2-Pyridinemethanethiol 1-Oxide (XXIII) Hydrochloride——To 23 ml. of anhydrous ethanol was added 0.34 g. of metallic sodium and then dry hydrogen sulfide gas was introduced till phenolphthalein indicator showed alkaline. To the solution was added a dry ethanolic solution of XIX liberated from 5 g. of XIX·HBr[5] on alkaline treatment. Precipitating sodium bromide was filtered off and the mother liquor was concentrated *in vacuo*. The gummy remainder was dissolved in 5 ml. of 4*N* ethanolic hydrogen chloride under warming. After removing the undissolved substance, 2,2'-dithiodimethyldipyridine 1,1'-dioxide hydrochloride, the mother liquor was concentrated to a small volume and ether added to cause precipitation.

*5 All melting and boiling points are uncorrected.

9) H. A. Adkins, A. A. Pavlic : J. Am. Chem. Soc., **69**, 3039 (1947).
10) R. R. Renshaw, M. Ziff, B. Brodie, N. Kornblum : J. Am. Chem. Soc., **61**, 638 (1939).
11) K. Winterfeld, K. Küllmar, W. Göhel : Ber., **92**, 1510 (1959).
12) E. S. Nikitaskaya : Zhur. obshcheĭ Khim., **29**, 124 (1959); C. A., **53**, 21931 (1959).
13) R. A. Barnes, H. M. Fales : J. Am. Chem. Soc., **75**, 975 (1953).

The precipitate was dissolved in warm ethanol again, filtered and ether added to deposit a solid mass. Filtration followed by recrystallization from acetone gave colorless pillars of m.p. 114~115°, yield 0.3 g. (9.1%). The whole treatment was persued in the stream of N_2 gas. The product was positive in the nitroprusside test for thiol group. *Anal.* Calcd. for $C_6H_7ONS \cdot HCl$ (XXIII·HCl) : C, 40.56; H, 4.54; N, 7.88. Found : C, 40.53; H, 4.45; N, 7.65.
Picrate : recrystallized from ethanol, m.p. 107~108°.

6-Methyl-2-pyridinemethanethiol 1-Oxide (XI) Hydrochloride——a) The preparation method of XXIII·HCl described above was applied here and a crude product of XI·HCl was derived from X. Recrystallization from ethanol gave colorless pillars of m.p. 133~134°, yield 21%, the nitroprusside test positive. *Anal.* Calcd. for $C_7H_9ONS \cdot HCl$ (XI·HCl) : C, 43.86; H, 5.26; N, 7.31. Found : C, 43.70; H, 5.28; N, 7.77. 2,2′-Dithiodimethyl-6,6′-dimethyldipyridine 1,1′-dioxide, m.p. 160~164°, was also produced and identified on a mixture melting point dertermination with an authentic sample described below.
b) A suspension of 0.2 g. of XX in 0.6 ml. of 2*N*-aqueous sodium hydroxide was heated on a water-bath for 2 hr. After cooling, the reaction mixture was acidified with ethanolic hydrochloric acid and concentrated to a small volume. Precipitating sodium bromide was filtered off and ether was added to the filtrate causing precipitation. The precipitate was repeatedly recrystallized from ether-ethanol to give colorless pillars of m.p. 132~133°, yield 0.02 g. (14.5%). A mixture with an authentic sample prepared under heading (a) showed no depression of melting point. The whole treatment was carried out in the stream of N_2 gas.

2,2′-Thiodimethyldipyridine 1,1′-Dioxide——The free base, XIX, liberated from 3 g. of its hydrobromide was added to 5 ml. of water containing 1.34 g. of sodium sulfide nonahydrate and heated on a water-bath for 2 hr. After cooling, the reaction mixture was extracted with chloroform, dried over anhyd. sodium sulfate and evaporated to dryness. The residue was recrystallized from methanol to give light yellow pillars of m.p. 174~175° (decomp.), yield 0.5 g. (36%). *Anal.* Calcd. for $C_{12}H_{12}O_2N_2S$: C, 58.07; H, 4.88; N, 11.28. Found : C, 58.25; H, 5.17; N, 10.99.
Picrate : recrystallized from ethanol. m. p. 148°.

2,2′-Thiodimethyl-6,6′-dimethyldipyridine 1,1′-Dioxide——X was treated just like the foregoing item giving a crude product. Recrystallization from ethyl acetate afforded light yellow pillars of m.p. 121~122°, yield 1.21 g. (35%). *Anal.* Calcd. for $C_{14}H_{16}O_2N_2S$: C, 60.84; H, 5.83; N, 10.14. Found : C, 60.85; H, 6.09; N, 10.07.
Hydrochloride : recrystallized from ethanol, colorless granules of m.p. 163~164° (decomp.).

2,2′-Dithiodimethyldipyridine 1,1′-Dioxide——a) An aqueous solution of sodium disulfide was prepared by mixing 1.34 g. of sodium sulfide nonahydrate and 0.23 g. of sulfur in 10 ml. of water. To the solution was added XIX liberated from 3 g. of its hydrobromide and heated on a water bath for 2 hr. After cooling, the reaction mixture was extracted with chloroform, dried over andyd. sodium sulfate and evaporated to dryness. The gummy residue was washed with ether and 3 ml. of 4*N*-ethanolic hydrochloric acid added causing crystallization of the residue. Filtration followed by recrystallization from methanol gave colorless pillars, m.p. 162~163° (decomp.), yield 0.3 g. (15%). *Anal.* Calcd. for $C_{12}H_{12}O_2N_2S_2 \cdot 2HCl$: C, 40.82; H, 3.97; N, 7.93. Found : C, 40.53; H, 4.24; N, 7.92.
Picrate : recrystallized from ethanol, m.p. 139~140°.
b) Air was bubbled into an ethanolic solution of XXIII overnight and the solution was evaporated to dryness. The residue was converted to picrate which was identical with an authentic sample prepared in heading (a), m.p. 135~139° and mixed m.p. 136°.

2,2′-Dithiodimethyl-6,6′-dimethyldipyridine 1,1′-Dioxide——a) Treatment of X was carried out exactly as heading (a) of the foregoing item. The crude product (hydrochloride) was recrystallized from ethanol to give colorless pillars of m.p. 192~193° (decomp.), yield 1.06 g. (28%). *Anal.* Calcd. for $C_{14}H_{16}O_2N_2S_2 \cdot 2HCl$: C, 44.09; H, 4.76; N, 7.35. Found : C, 43.76; H, 4.86; N, 7.39.
b) Oxidation of XI with air was carried out just like procedure (b) of the foregoing item. The resulting product was converted to hydrochloride in the usual way, which was recrystallized from ethanol affording colorless pillars, yield 38.5%, m.p. 192~193° (decomp.) alone and on admixture with a sample prepared in heading (a).

2-Ethylthiomethylpyridine 1-Oxide (XXIV)——The free base generated from 2.8 g. of XIX·HBr was added to 40 ml. of water containing 2.7 g. of sodium ethanethiolate and stirred for 2 hr. The solution was salted out with sodium chloride, extracted with chloroform several times, dried over anhyd. sodium sulfate and evaporated to dryness. The residue was distilled *in vacuo* yielding 0.5 g. (30%) of a yellowish oil, $b.p_6$ 134~137°. The oil was converted to picrolonate which was recrystallized from ethanol, m.p. 137°. *Anal.* Calcd. for $C_8H_{11}ONS \cdot C_{10}H_8O_5N_4$ (XXIV·picrolonate) : C, 49.88; H, 4.42; N, 16.17. Found : C, 49.95; H, 4.54; N, 16.02.

2-Ethylthiomethyl-6-methylpyridine 1-Oxide (XII)——The reaction of X with sodium ethanethiolate was carried out just like the foregoing item to yield XII as a yellow oil, $b.p_3$ 143~146°, yield 39%.
Picrolonate : recrystallized from ethanol, m.p. 120.5~121°. *Anal.* Calcd. for $C_9H_{13}ONS \cdot C_{10}H_8O_5N_4$ (XII·picrolonate) : C, 51.00; H, 4.73; N, 15.88. Found : C, 51.35; H, 4.97; N, 15.62.

Treatment of 2-Bromomethyl-6-methylpyridine 1-Oxide (X) with Acetic Anhydride——One gram of X in 5 ml. of acetic anhydride was refluxed for 4 hr. and concentrated *in vacuo*. The residue was neutralized with aqueous potassium carbonate, extracted with chloroform, dried over anhyd. sodium sulfate and befreed of the solvent. Vacuum distillation gave 0.5 g. of a pink oil, b.p_2 90~115°. The distillate was added to 10 ml. of 47% aqueous hydrobromic acid and refluxed for 4 hr. The solution was concentrated *in vacuo* and the oily remainder was dissolved in a small volume of warm ethanol. After cooling, crystals precipitated and were collected by filtration, yield 0.28 g. (39.6%), m.p. 208~210° (decomp.) after recrystallization from ethanol. Melting point was undepressed on admixture with an authentic sample of 2,6-bis(bromomethyl)pyridine hydrobromide (XVIII·HBr),[4] m.p. 210~211° (decomp.). To the ethanolic filtrate was added a solution of 2,4-dinitrophenylhydrazine in aqueous phosphoric acid to cause the precipitation of crystals which were identical with IX[3] 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 231~233° (decomp.).

Treatment of 6-Methyl-2-pyridinemethanethiol 1-Oxide (XI) with Acetic Anhydride——The free base generated from XI·HCl was added to 5 ml. of acetic anhydride and refluxed in the stream of N_2 gas for 3 hr. The reaction mixture was concentrated *in vacuo* and neutralized with aqueous potassium carbonate, extracted with chloroform four times, dried over anhyd. sodium sulfate and evaporated to dryness. Vacuum distillation of the residue gave 0.2 g. (21%) of a yellow oil, b.p_5 112~114°, which was converted to picrolonate, m.p. 164° (decomp.) after recrystallization from ethanol. The picrolonate was identical with 6-methyl-2-pyridinemethanethiol acetate (XVI) picrolonate described below on a mixture melting point determination.

6-Methyl-2-pyridinemethanethiol Acetate (XVI)——To a suspension of 0.1 g. of powdered metallic sodium in dry ether was dropwise added 0.38 g. of thiolacetic acid under ice-chilling and stirring. Furthermore, 0.8 g. of 6-methyl-2-bromomethylpyridine (XXXI)[4] dissolved in 5 ml. of dry ether was added and stirred for 2 hr. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was distilled under reduced pressure to give 0.41 g. of a yellow oil, b.p_5 112~114°.
Picrolonate : recrystallized from ethanol, m.p. 164~165° (decomp.). *Anal.* Calcd. for $C_9H_{11}ONS \cdot C_{10}H_8O_5N_4$: C, 51.22; H, 4.29; N, 15.73. Found : C, 51.47; H, 4.42; N, 15.41.

Treatment of 2-Ethylthiomethyl-6-methylpyridine (XII) with Acetic Anhydride——A solution of 3 g. of XII in 9 ml. of acetic anhydride was refluxed for 4 hr. The reaction mixture was concentrated *in vacuo*, neutralized with aqueous potassium carbonate, extracted with chloroform, dried over anhyd. sodium sulfate and evaporated to dryness. Vacuum distillation gave 3.4 g. (84.2%) of a pink oil, b.p_5 143~144°.
Picrate : recrystallized from aqueous ethanol, m.p. 105~107°. *Anal.* Calcd. for $C_{11}H_{15}O_2NS \cdot C_6H_3O_7N_3$ (6-ethylthio-6-methyl-2-pyridinemethanol acetate (XVII) picrate) : C, 44.93; H, 3.99; N, 12.33. Found : C, 44.76; H, 4.32; N, 12.13. To 1 g. of the pink oil was added 20 ml. of 20% aqueous hydrochloric acid and refluxed in the stream of N_2 gas for 10 hr. Evolving gas was absorbed in 15% ethanolic sodium hydroxide and the existence of ethanethiol in the ethanolic solution was proven by the conversion to 2,4-dinitroethylthiobenzene, m.p. 72°. The hydrochloric acid solution was concentrated *in vacuo*, neutralized with aqueous potassium carbonate, extracted with chloroform, dried over anhyd. sodium sulfate and evaporated to dryness. Vacuum distillation furnished 0.46 g. (85.5%) of an oil b.p_{12} 77~78°, which was converted to 2,4-dinitrophenylhydrazone, m.p. 230°, alone and on admixture with an authentic sample of IX 2,4-dinitrophenylhydrazone.

2,2′-Oxydimethyldipyridine 1,1′-Dioxide (XXVI)——a) To 1 g. of XIX·HBr dissolved in 5 ml. of water was added 6 ml. of 2*N* aqueous sodium hydroxide and set aside at room temperature for 1 hr. depositing crystals. The reaction mixture was saturated with sodium chloride and allowed to stand overnight. Filtration followed by recrystallization from ethyl acetate gave colorless needles of m.p. 128~129°, yield 0.41 g. (88.3%), IR λ_{max}^{Nujol} μ : 8.73, 8.10. *Anal.* Calcd. for $C_{12}H_{12}O_3N_2 \cdot H_2O$ (XXVI·H_2O) : C, 57.59; H, 5.64; N, 11.19; mol. wt. 250.25. Found : C, 57.29; H, 5.80; N, 11.14; mol. wt. (Rast) 250.7.
Picrate : recrystallized from ethanol, m.p. 192~193°. *Anal.* Calcd. for $C_{12}H_{12}O_3N_2 \cdot C_6H_3O_7N_3$ (XXVI·picrate) : C, 46.86; H, 3.28; N, 15.18. Found : C, 46.97; H, 3.38; N, 15.11.
b) A mixture of 0.2 g. of 2,2′-oxydimethyldipyridine (XXVIII), 2 ml. of acetic acid and 0.4 ml. of 30% hydrogen peroxide was heated at 70~80° for 12 hr. The reaction mixture was evaporated, added 3 ml. of water and again evaporated to a small volume. Addition of acetone to the aqueous solution caused precipitation of crystals. Filtration followed by recrystallization from ethyl acetate gave colorless needles of m.p. 127°, yield 0.1 g. (43.2%), which showed no depression of melting point on admixture with a sample of XXVI·H_2O prepared by procedure (a).

Treatment of XXVI with Hydrobromic Acid. The Formation of XIX——A solution of 0.3 g. of XXVI in 15 ml. of 48% hydrobromic acid was refluxed for 7 hr. and evaporated to dryness *in vacuo*. The residue was converted to picrate in the usual way, which was identical with XIX[5] picrate, m.p. 129~130°.

2,2′-Oxydimethyldipyridine (XXVIII)——a) To 0.4 g. of XXVI in 30 ml. of chloroform was added 0.3 ml. of phosphorus trichloride and heated on a water bath for 1 hr. The solution was made alkaline with aqueous potassium carbonate, extracted with chloroform, dried over anhyd. sodium sulfate and evaporated to dryness. Vacuum distillation furnished 0.23 g. (72%) of an oil, b.p_4 146~148°.

Picrate : recrystallized from ethanol, m.p. 197～198° (decomp.). *Anal.* Calcd. for $C_{12}H_{12}ON_2 \cdot 2C_6H_3O_7N_3$ (XXVIII·dipicrate) : C, 43.78; H, 2.76; N, 17.02. Found : C, 44.14; H, 3.01; N, 16.97.

b) To a solution of 2 g. of XXX in 10 ml. of xylene was added 5.4 g. of conc. sulfuric acid under stirring and ice-cooling and heated at 160～170° for 5 hr. to remove water formed by an azeotropic mixture with xylene. The remainder was made alkaline with aqueous potassium carbonate while ice-cooling, extracted with chloroform, dried over anhyd. sodium sulfate, and evaporated to dryness. The residue was separated to two fractions by vacuum distillation, $b.p_8$ 100～105° and $b.p_3$ 145～148°, yield 1.6 g. and 0.22 g. respectively. The distillates were converted to picrates, of which the first was identical with XXX·picrate, m.p. 160～161° and the second, m.p.197°, showed no depression of melting point on admixture with a sample prepared by procedure (a).

c) To 10 ml. of 2*N*-aqueous sodium hydroxide was added lg. of XXXII·HBr and stirred for 5 hr. forming two layers. The mixture was extracted with chloroform, dried over anhyd. sodium sulfate and evaporated to dryness. The residue was separated to two fractions by vacuum distillation, $b.p_4$ 74～80° and $b.p_4$ 80～124°, yield 0.21 g. and 0.23 g. respectively. The picrate of the first distillate was identical with XXX·picrate, m.p. 160～161°, and the picrate of the second melted at 197° without depression of melting point on admixture with a sample prepared by procedure (a).

2,2′-Oxydimethyl-6,6′-dimethyldipyridine 1,1′-Dioxide (XXV)——a) Treatment of X was carried out just like method (a) for the preparation of XXVI and a resulting crude product was recrystallized from methanol yielding colorless needles of m.p. 175～177°, yield 82.3%. *Anal.* Calcd. for $C_{14}H_{16}O_3N_2 \cdot \frac{1}{2}H_2O$ (XXV) : C, 62.44; H, 6.36; N, 10.40; mol. wt. 269.3. Found : C, 62.83; H, 6.32; N, 10.29; mol. wt. (Rast) 276.

Picrate : recrystallized from ethanol, m.p. 174～175°. *Anal.* Calcd. for $C_{14}H_{16}O_3N_2 \cdot 2C_6H_3O_7N_3$ (XXV·dipicrate) : C, 43.46; H, 3.09; N, 15.60. Found : C, 43.57; H, 3.13; N, 15.89.

b) Method (b) for the preparation of XXVI was similarly applied to the conversion of XXVII to XXV. The product was yielded at 78.5% and identical with a sample of XXV prepared by procedure (a) of this item, m.p. 175～177°.

2,2′-Oxydimethyl-6,6′-dimethyldipyridine (XXVII)——This compound was prepared from each of XXIX and XXXI in application of methods (b) and (c) for the preparation of XXVIII respectively. Method (b) gave two fractions by vacuum distillation, $b.p_4$ 85～95° and $b.p_4$ 150～155°. The first fraction was converted to the picrate which was identical with XXIX picrate,[1] m.p. 130～132°, on a mixture melting point determination. The second fraction, yield 33.8%, was converted to the picrate which was recrystallized from ethanol, m.p. 210～212° (decomp.), *Anal.* Calcd. for $C_{14}H_{16}ON_2 \cdot 2C_6H_3O_7N_3$ (XXVII·dipicrate) : C, 45.49; H, 3.23; N, 16.32. Found : C, 45.38; H, 3.37; N, 16.41. Method (c) gave a substance which melted at 75～76°, yield 63.2%, after recrystallization from water. The picrate melted at 210～212° (decomp.) alone and on admixture with a sample of XXVII·dipicrate prepared by method (b).

Treatment of 2,2′-Oxydimethyldipyridine 1,1′-Dioxide (XXVI) with Acetic Anhydride——A mixture of 5 g. of XXVI and 30 ml. of acetic anhydride was refluxed for 4 hr. and then concentrated *in vacuo*. The residue was submitted to fractional distillation yielding two fractions. The first fraction was a colorless oil, $b.p_3$ 118～123°, yield 1.4 g. (15.5%).

Picrate : recrystallized from ethanol, m.p. 146～147° alone and on admixture with picolinaldehyde diacetate picrate.[1] The second fraction was a yellow oil, $b.p_{0.1}$ 150～156°, yield 2.15 g. (46.6%), which was redistilled *in vacuo* effecting solidification, $b.p_{0.05}$ 155～157°. After recrystallization from ligroin, it melted at 52～53° and showed no depression of melting point on admixture with a sample of 2-pyridylmethyl picolinate described below. The structure of this compound was also confirmed by hydrolysis which gave 2-pyridylmethanol and 2-pyridinecarboxylic acid.

2-Pyridinemethanol Picolinate——To a solution of 1.6 g. of picolinic acid in 3 ml. of benzene was added 6 g. of conc. sulfuric acid and then 1.1 g. of 2-pyridinemethanol under ice-cooling and stirring. While adding anhyd. benzene in drops, the mixture was heated on a water-bath for 6 hr. to remove benzene-water. The charge was slowly poured on ice and made alkaline with aqueous potassium carbonate. The benzene layer was separated and the aqueous layer was extracted with benzene. The combined benzene solution was dried over anhyd. sodium sulfate and evaporated to dryness. Fractional distillation of the residue gave a colorless oil of $b.p_{0.3}$ 46°, yield 0.5 g. and a yellowish oil of $b.p_{0.3}$ 130°, yield 0.26 g. (8.1%). The picrate of the colorless oil, m.p. 155～157°, was identical with XXX·picrate. The yellowish oil crystallized while chilling and melted at 52～53° after recrystallization from ligroin. *Anal.* Calcd. for $C_{12}H_{10}O_2N_2$ (2-pyridylmethyl picolinate) : C, 67.3; H, 4.67; N, 13.0. Found : C, 67.34; H, 4.78; N, 13.11.

Picrate : recrystallized from ethanol, m.p. 155～157°.

DL-2-Piperidinemethanol (XXXIII)——A solution of 50 g. of XXX in 50 ml. of ethanol was placed in an autoclave with 50 ml. of Raney Ni W-2. The initial pressure in the bomb was raised to 200 kg./cm² and heated at 80° while agitating. The reaction was allowed to proceed for 7 hr., during which time the theoretical amount of H_2 was nearly absorbed. The catalyst was removed from the reaction mixture by filtration and the filtrate was evaporated to dryness. The residue was distilled *in vacuo* to give 47.8 g. (90.7%) of a colorless oil, $b.p_{13}$ 108°.

Picrate : recrystallized from ethanol, m.p. 133～135°. The picrate showed no depression of melting point

on admixture with an authentic sample of XXXIII picrate.[9~11]

***Meso-cis*-2,6-Piperidinedimethanol (XXXIV)**——a) A mixture of 1 g. of dimethyl *meso-cis*-2,6-piperidinedicarboxylate[13] (XXXVI), 0.5 g. of $LiAlH_4$ and 40 ml. of ether was refluxed for 3 hr. To the reaction mixture was added water to decompose remaining $LiAlH_4$. After removal of ether, the mixture was extracted with pyridine, dried over anhyd. potassium carbonate and evaporated to leave crystals. Recrystallization from ethyl acetate furnished colorless plates of m.p. 130~131°, yield 1.5 g. (70.1%). *Anal.* Calcd. for $C_7H_{15}O_2N$ (XXXIV): C, 57.90; H, 10.41; N, 9.65. Found: C, 57.88; H, 10.40; N, 9.65.

b) Hydrogenation of 4 g. of VIII over 10 ml. of Raney Ni W-2 was carried out in 20 ml. of ethanol just like the case of XXX to yield a crystalline product. The product was recrystallized from ethyl acetate to give colorless plates, m.p. 130~131°, yield 3.4 g. (81.6%) which were identical with XXXIV prepared by method (a) on a mixture melting point determination.

c) Hydrogenation of 3.5 g. of dimethyl 2,6-pyridinedicarboxylate (XXXV) over 15 ml. of Raney Ni W-2 was persued in 35 ml. of methanol exactly as procedure (b). Isolation followed by purification was also done just like procedure (b) to afford colorless plates of m.p. 128~130°, yield 2.2 g. (82.6%), which was identical with a sample prepared by method (a) on a mixture melting point determination.

d) A product yielded by tracing the Nikitaskaya's procedure,[12] m.p. 130~131°, showed no depression of melting point on admixture with a sample prepared by method (a).

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Summary

Syntheses of DL-2-piperidinemethanol (XXXIII) and *meso-cis*-2,6-piperidinedimethanol (XXXIV) were accomplished through a few steps from 2-picoline (I) and 2,6-lutidine (II) respectively. The configuration of XXXIV was confirmed. The following reactions of synthetic intermediates were also examined. 6-Methylpicolinaldehyde (IX) was obtained by acetolysis followed by hydrolysis from 2-bromomethyl-6-methylpyridine 1-oxide (X) through α-bromo-6-methyl-2-pyridinemethanol acetate (XIV) in a yield, 16.2% and from 2-ethylthiomethyl-6-methylpyridine 1-oxide (XII) through α-ethylthio-6-methyl-2-pyridinemethanol acetate (XVII) in a yield, 84.2%. Unusually enough, alkaline treatment at room temperature converted 2-bromomethylpyridine 1-oxide (XIX) to 2,2′-oxydimethyldipyridine 1,1′-dioxide (XXVI) in a yield as high as 88.3%. The ether formation was found in the same treatment of analogues.

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