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Organometallic Compounds. XV.[1] Synthesis and Stereochemistry of 1',2',5',6'-Tetrahydro-2'-methylpyrido(3',4')ferrocene Isomers[2]

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Reduction of the methoiodide (IV) with $NaBH_4$ gave predominantly *endo*-2'-methyl compound (Va). On the other hand, the reaction of VII with methyl magnesium iodide gave *exo*-2'-methyl compound (Vb). Configuration and conformation of *endo*- and *exo*-2'-methyl-tetrahydropyridoferrocene (Va and Vb) and its quaternary salt (VIa and VIb) were discussed by means of conformational analysis and nuclear magnetic resonance spectroscopy.

Attempted synthesis of pyridoferrocene (X) from XIII was unsuccessful.

Nitrogen containing ferrocene derivatives[4] such as tetrahydropyrido(3',4')ferrocene (I) are interesting compounds in regard to the physiological activities of analogous tetrahydroisoquinoline derivatives.

The synthesis of 1',2',5',6'-tetrahydro-2'-methylpyrido(3',4')ferrocene (III) by reduction of 5',6'-dihydro-2'-methylpyrido(3',4')ferrocene (II) with $LiAlH_4$ was first described by Osgerby and Pauson.[5] Two stereoisomers, *endo*- and *exo*-2'-methyl derivatives IIIa and IIIb, are the possible components of compound III, but they could not be separated by the chromatography of III, which was obtained as a single crystalline picrate.

Furthermore, these tetrahydromethylpyridoferrocenes present interesting stereochemical problems due to the ferrocene chirality,[6] when such a stereochemical problem is not to be found with 1-methyltetrahydroisoquinoline analogous.

In this paper, we wish to report syntheses of 1',2',5',6'-tetrahydro-1',2'-dimethylpyrido-(3',4')ferrocene isomers (Va and Vb) and related compounds; then the stereochemistry of these isomers are discussed.

We reinvestigated the reduction of II with $LiAlH_4$, according to the procedure of Pauson, *et al.*,[5] and obtained an oily yellow-brownnish product, with 90% yield. The nuclear magnetic resonance (NMR) spectra of the product indicated that the signals of 2'-methyl appeared as a doublet at δ 1.47 and a doublet at δ 1.18 in a ratio of 7:1. The 2'-methine proton corresponding to the 2'-methyl protons (δ 1.47) appeared as a quartet at δ 3.48. On this basis we assigned to the two methyl derivatives the epimeric structures IIIa and IIIb. The structure of the main reduction product, which shows the NMR signals at δ 1.47 (methyl protons) and δ 3.48 (methine proton), was assummed to be the *endo*-2'-methyl isomer (IIIa) on the basis of the NMR spectroscopy and the reduction mechanism. The chemical shift of IIIa, a doublet *endo*-2'-methyl protons, should appear at a lower field ($\Delta\delta$ 0.29) than the *exo*-2'-methyl epimer (IIIb), this being due to the aromatic ring anisotropic effect of the ferrocene nucleus.[7,8]

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1) Part XIV: M. Hisatome, S. Minagawa, and K. Yamakawa, *J. Organometal. Chem.*, **55**, C82 (1973).

2) Taken in part from the Master Thesis of K. Osumi, Science University of Tokyo, March 1968.

3) Location: *Ichigayafunagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*

4) For review see, F.D. Popp and E.B. Moynahan, "Advances in Heterocyclic Chemistry," Vol. 13, Academic Press, New York, 1972, pp. 1—44.

5) J.M. Osgerby and P.L. Pauson, *J. Chem. Soc.*, **1961**, 4600.

6) K. Schlögl in Allinger and Eliel Ed., "Topics in Stereochemistry," 1, Interscience Publishers, New York, 1967, pp. 39—91.

7) T.D. Turbitt and W.E. Watts, *Tetrahedron*, **28**, 1227 (1972).

8) K. Yamakawa and M. Hisatome, *Tetrahedron Letters*, **1967**, 2827.

The stereoformula of IIIa is also supported by the reduction mechanism. The $LiAlH_4$ complex is further attacked from the less hindered upper side of the fused ferrocene ring. Thus the predominant formation of the *endo*-2′-methyl isomer (IIIa) is explicable by the hydride attack at 2′-carbon atom from the least hindered exoside of the ring as depicated in the Chart.

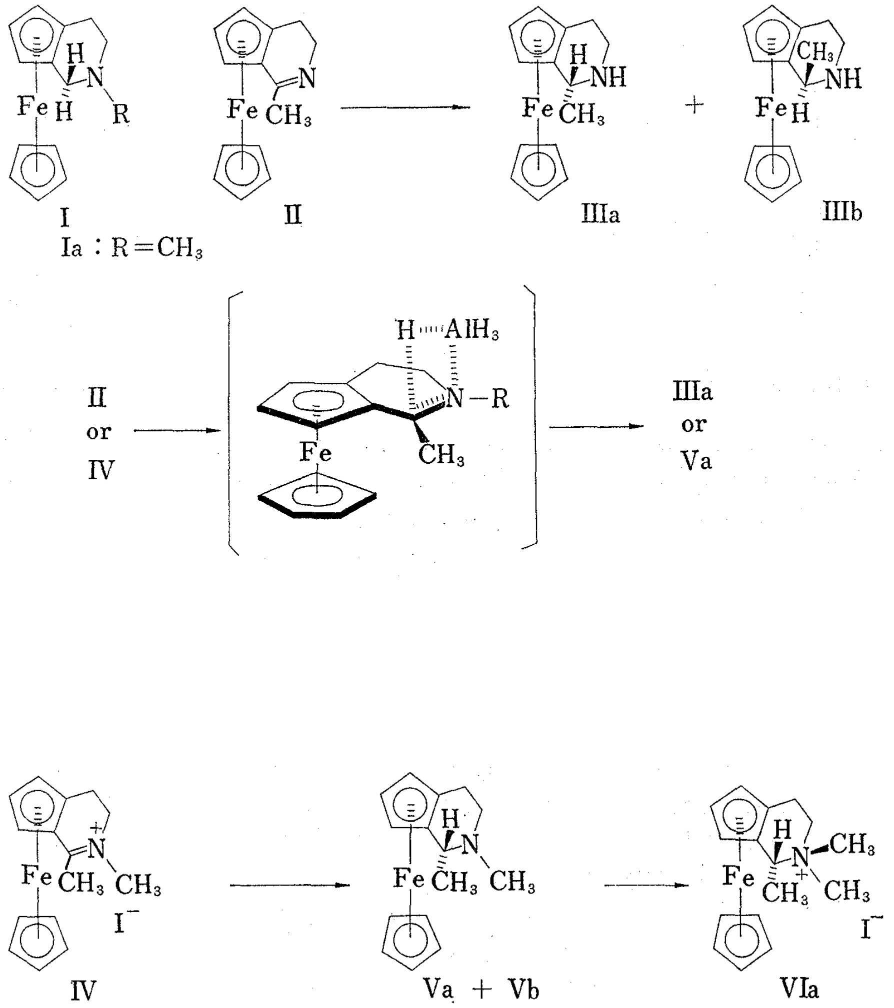

Chart 1

However, the tetrahydro compounds IIIa and IIIb suffer autooxidation easily, and go back to the starting dihydro compound (II) on column chromatography with basic alumina. Consequently, our work was directed towards more stable compounds like N-methyl derivatives.

Reduction of the methoiodide of the dihydro compound (II) with $NaBH_4$ gave a mixture of tetrahydro-1′,2′-dimethylpyrido(3′,4′)ferrocene (Va and Vb) as a yellow oil with 85% yield. The NMR spectra of the reduced dimethyl products showed a doublet of the 2′-methyl protons at δ 1.50 and δ 1.20, in the intensity ratio of 11: 1. In this case, according to the above mentioned NMR spectrometry and the stereospecific reduction mechanism, the predominant product was assumed to be the 2′-methyl *endo*-isomer (Va). Through similar conditions the minor product was assumed to be the 2′-methyl *exo*-isomer (Vb). The chemical shift of the *endo*-2′-methyl hydrogen of the main product (Va) appeared as a doublet at δ 1.50 and that of the corresponding *exo*-2′-hydrogen as a quartet at δ 2.83 using the double resonance techniques; the minor product showed a doublet of the *exo*-2′-methyl protons at δ 1.20. The NMR spectra of the pure samples of Va and Vb are shown in Fig. 1.

The above reduction products (V) were converted to the methoiodide (VIa), which was recrystallized as yellow plates, mp 216—219° (dec.).

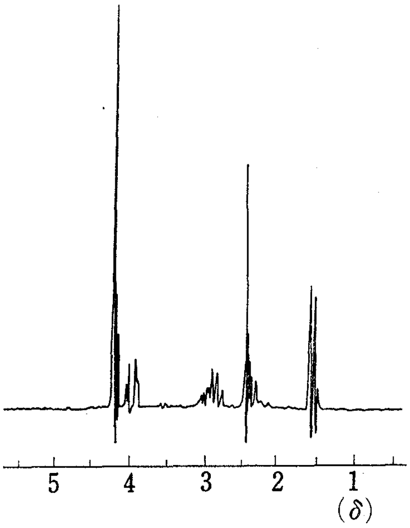

Fig. 1a. NMR Spectrum of Va

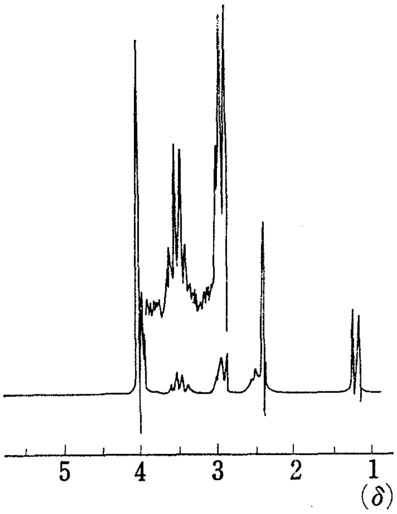

Fig. 1b. NMR Spectrum of Vb

The minor compound *exo*-2′-methyl isomer (Vb) was prepared from N-methyldihydro compound (VII) with methyl magnesium iodide. Such a product was expected, because the bulky Grignard reagent should attack the C=N linkage from the upper side of the fused ring system. The reaction of VII with methyl magnesium iodide in ether solution gave a yellow brown oily product in 85% yield, which shows disappearance of the C=N absorption band at 1610 cm^{-1} in infrared (IR) spectrum. The NMR spectrum showed as we expected a strong doublet at δ 1.20 for the *exo*-2′-methyl protons and a weak signal of *endo*-2′-methyl doublet at δ 1.50, the signal intensity ratio being 15: 1. From the above results we can state that methylation reaction occured with a high stereospecificity. The chemical shift of a doublet methyl signal coincide with the NMR spectrum of the reduction product of 5′,6′-dihydro-1′,2′-dimethylpyrido(3′,4′)ferrocene (IV) with $NaBH_4$. The 2′-methine proton showed a quartet at δ 3.52 which is 0.69 ppm lower than that of the previously assumed *exo*-2′-methine proton (δ 2.83) due to the aromatic ring current anisotropic effect of ferrocene moiety. According to the stereospecific reaction mode and the NMR spectrometry the structure of the methylation main product can be established as 1′,2′,5′,6′-tetrahydro-*exo*-2′-methyl-N-methylpyrido-(3′,4′) ferrocene (Vb). Vb was converted into a crystalline methoiodide (VIb) as yellow brown plates, mp 230—235° (dec.).

On the other hand, methylation of the dimethyl compound (IV) with methyl magnesium iodide in ether was carried on. A yellow brown oily product was obtained in a lower (25%) yield, which shows a disappearance of the C=N absorption band at 1615 cm^{-1} in the IR spectrum, and give rise to two methyl signals as singlet at δ 1.53 and δ 1.15 in the NMR spectrum. The structure of this product is to be assigned as 1′,2′,5′,6′-tetrahydro-2′,2′-dimethyl-N-methylpyrido(3′,4′)ferrocene (VIII). VIII was converted into a crystalline methoiodide (IX) as yellow plates, mp 172—175° (dec.).

The chemical shifts of *endo*- and *exo*-2′-methyl compounds (Va, δ 1.50 and Vb, δ 1.20) were in good coincidence with the corresponding chemical shifts of *endo*- and *exo*-methyl (δ 1.53 and 1.15) of 2′,2′-*gem*-dimethyl derivative (VIII), respectively.

Pauson, *et al.*⁵⁾ and Popp and Moynahan⁹⁾ attempted the synthesis of pyridoferrocene (X: $R=CH_3$ or H) from the dihydro compound, as attempted with isoquinoline analogous, but they were not successful.

We also attempted the synthesis of Xa by alternative route as follows: a hydroxyl group was introduced into the α-position of ferrocenyl moiety in the Bishler–Napieralski reaction

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9) F.D. Popp and E.B. Moynahan, 3rd International Congress of Heterocyclic Chemistry, Abstracts of Papers pp. 577—578, Aug. 23—27, 1971, Sendai, Japan.

step, then α-hydroxylamine (XII) and its acetyl derivative (XIIIa) were synthesized as intermediated from the formylferrocene cyanhydrin (XI).[10] Reduction of XI with $LiAlH_4$ afforded 1-hydroxy-2-aminoethylferrocene (XII) as golden yellow plates in 80% yield, mp 166—167°. By acetylation of XII was predominantly converted into the acetylamino derivative (XIIIa) as yellow brown plates, mp 128—129°. The structure of XIIIa was demonstrated by IR and NMR spectrometry: it shows an amido I band at 1640 and 1560 cm^{-1} and no absorption in the O-acetyl band of the IR spectrum; in the NMR spectrum an acetyl methyl signal was present at δ 2.00 and an amido NH broading signal at δ 6.35.

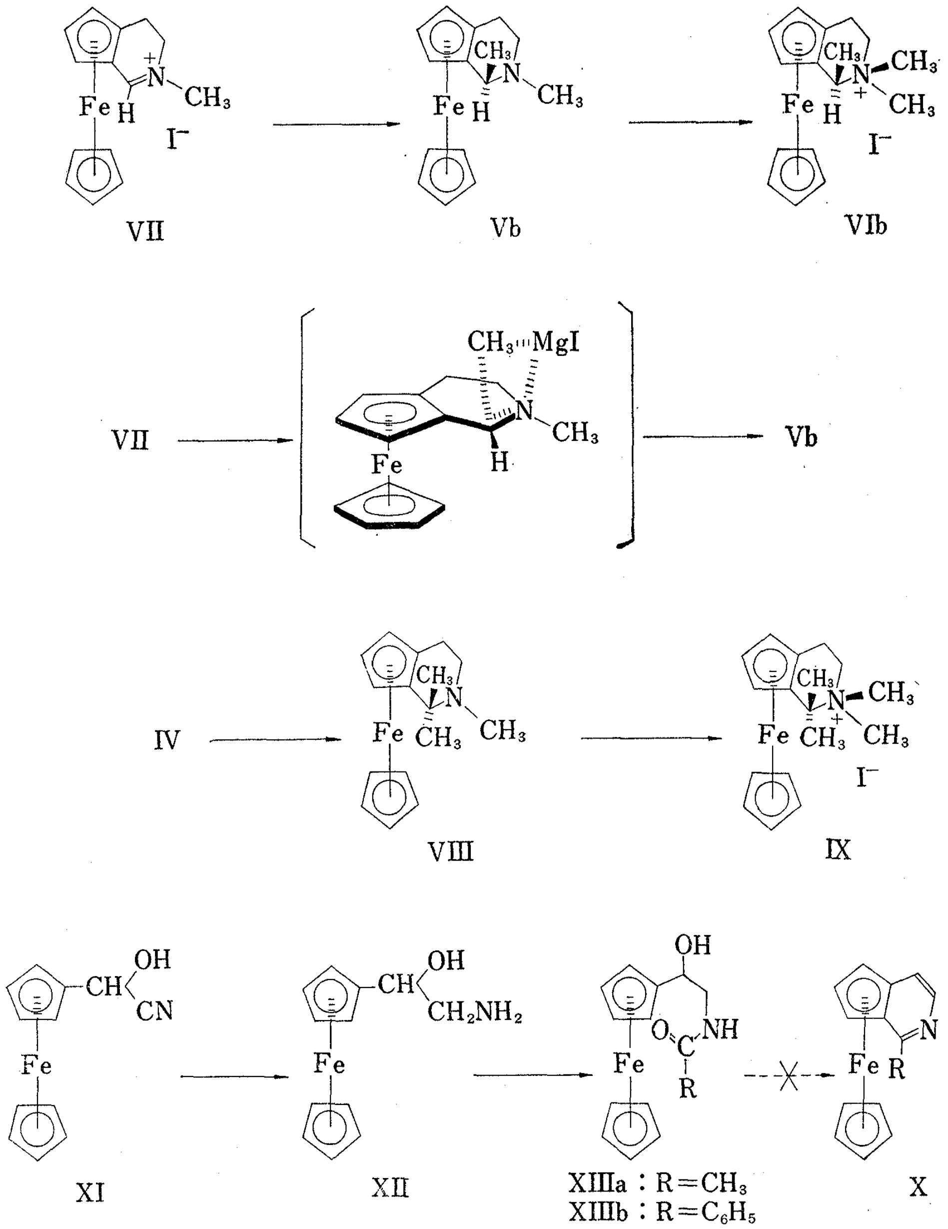

Chart 2

We attempted the synthesis of 2′-methylpyrido(3′,4′)ferrocene (Xa) from XIII using the Bishler–Napieralski reaction. But even though we used different reagents we failed to obtain this isoquinoline analogous (X) this probably being due to the decomposition.

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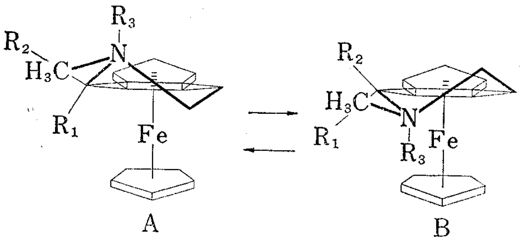
[10] P.J. Graham, R.V. Lindsay, G.W. Parshall, M.L. Peterson, and G.W. Shitman, *J. Am. Chem. Soc.*, 79, 3416 (1957).

Table I. ^{1}H NMR Spectra of N-Methyltetrahydropyrido(3′,4′)ferrocene Derivatives ($CDCl_3$; δ values ppm)

Compounds	$C_{2'}$-H (exo)	$C_{2'}$-H (endo)	$\Delta\delta$	$C_{2'}$-CH_3 (exo)	$C_{2'}$-CH_3 (endo)	$\Delta\delta$	N-CH_3 (exo)	N-CH_3 (endo)	$\Delta\delta$
Ia	3.40(d)	3.50(d) (J =13.5Hz)	0.10	—	—	—	—	2.42(s)	—
CH_3I salt of Ia	4.26(d)	4.72(d) (J =13.5Hz)	0.46	—	—	—	2.86(s)	3.36(s)	0.50
Va	2.83(q) (J =6.5Hz)	—	0.69	—	1.50(d) (J =65Hz)	0.30	2.42(s)		0.00
Vb	—	3.52(q) (J =6.5Hz)		1.20(d) (J =6.5Hz)	—			2.42(s)	
VIa	4.27(q) (J =6.5Hz)	—	0.77	—	1.79(d) (J =6.5Hz)	0.35	3.13(s)	3.37(s)	0.24
VIb	—	5.04(q)		1.44(d)	—		2.63(s)	3.30(s)	0.67
VIII	—	—	—	1.15(s)	1.53(s)	0.38		2.38(s)	
IX	—	—	—	1.47(s)	1.99(s)	0.52	2.84(s)	3.31(s)	0.47

The chemical shifts of the N-methyl compounds and their methoiodides prepared in this investigation are listed in the Table. These spectral data are able to illustrate by the diamagnetic anisotropy of the ferrocene molecule, which the existence of shielding and deshielding regions are proposed by Turbitt and Watts.[7]

Comparison of the spectra of the N-methyl compounds (Ia; Va, b; VIa, b; VIII and IX) established that the resonance of a $C_{2'}$-substituent occurs at higher field when the group or atom is attached in the *exo* configuration. For example, in the spectra of Va and Vb, the proton of $C_{2'}$-methine (Va) and the protons of an *exo* $C_{2'}$-methyl group (Vb) resonate at 0.69 and 0.30 ppm higher field than those of the *endo* $C_{2'}$-methine (Vb) and methyl (Va), respectively. Similarly, the spectra of the methoiodides (VIa and VIb) show that the exo hydrogen of the $C_{2'}$-methine and those of the *exo* methyl group resonate at higher field than those of the corresponding *endo* group (see Table).



Ia : $R_1=R_2=H$; R_3=lone pair
CH_3I salt of Ia: $R_1=R_2=H$; $R_3=CH_3$
Va : $R_1=CH_3$; $R_2=H$; R_3=lone pair
Vb : $R_1=H$; $R_2=CH_3$; R_3=lone pair
VIa : $R_1=R_3=CH$; $R_2=H$
VIb : $R_1=H$; $R_2=R_3=CH_3$
VIII : $R_1=R_2=CH_3$; R_3=lone pair
IX : $R_1=R_2=R_3=CH_3$

Chart 3. Conformations of N-Methyltetrahydropyridoferrocenes

The N-methyl-1′,2′,5′,6′-tetrahydropyridine ring may have a half-chair conformation fused with a cyclopentadienyl ring. N-Methyl groups of the free bases (Ia, Va and b, and VIII) are expected to possess equatorial orientation, taking into account the preferred conformation of N-methylpiperidines.[11] Considering preferred conformation of N-methyltetrahydropyrido(3′,4′)-ferrocenes on the basis of the stereomodels,[12] the most preferred conformations in the *exo*- and *endo*-substituents are expected to be two conformer A and B, which are interconversible by ring inversion of half-chair tetrahydropyridine rings. It is assumed that a bulky *exo* $C_{2'}$-substituent causes a displacement of the 1′-nitrogen atom away from the iron atom (conformer A) whereas a bulky *endo* $C_{2'}$-substituent produces a displacement in the opposite direction (conformer B).

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[11] E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis," Interscience Publishers, 1965, p. 252.

[12] H.G.S. and Dreiding ferrocene stereomodels supplied by Maruzen Co., Tokyo and by Büchi Glasapparatefabrik, Switzerland were used.

It may be suggested from the above NMR results and conformational analysis that the exo or endo methyl group possesses a quasi-equatorial orientation at $C_{2'}$ carbon atom. Then, preferred conformations of Vb and Va must be conformer A and conformer B, respectively.

The methoiodides of Va and Vb (VIa and VIb) are also provided as similar as preferred conformations of the free bases (Va and Vb) by means of the NMR data (see Table).

While, the methoiodides Ia and VIII (IX) show moderate values ($\Delta\delta$ 0.50 and 0.47) of N,N-dimethyl groups among the compound VIb and VIa ($\Delta\delta$ 0.67 and 0.24). Which results show the preferred conformation of the methoiodides of Ia and VIII (IX) may be an equilibrium of conformer A and B due to ring inversion, or it may exist an intermediary conformation between conformer A and B.

More detail conformational studies of the N-methylpyrido(3',4')ferrocenes and the other homoannularly bridged ferrocene derivatives by means of NMR spectrometry are in progress.

Several pharmacological activities of tetrahydropyridoferrocene derivatives were tested, but unfortunately they did not show any characteristic activity.

Experimental

All melting points were measured on a Yanagimoto melting point apparatus, and were uncorrected. IR spectra were taken on a Hitachi EPI-S2 spectrophotometer, and NMR spectra were measured with a Varian A-60 (60 MHz) and JEOL-JNM-4H-100 (100 MHz) spectrometer with tetramethylsilane as internal standard.

1',2',5',6'-Tetrahydro-2'-methylpyrido(3',4')ferrocene (IIIa and IIIb)——According to the procedure of Pauson, *et al.*,[5] a solution of the 5',6'-dihydro-2'-methylpyrido(3',4')ferrocene (II) (200 mg) in ether was added to an excess of ethereal $LiAlH_4$, and the mixture refluxed for 2 hr. After decomposition with water, the organic layer was separated, dried, and evaporated, leaving a yellow brown oil (180 mg; 90%).

In order to purify them, the above products were treated on alumina column chromatography, but only the starting dihydro compound (II) was recovered due to auto-oxidation occuring in the meanwhile.

1',2',5',6'-Tetrahydro-*endo*-2'-methylpyrido(3',4')ferrocene (Va)——a) To a solution of 5',6'-dihydro-2'-methylpyrido(3',4')ferrocene methoiodide (IV) (1.12 g) in ethanol, $NaBH_4$ (100 mg) was added, and the solution stirred at room temperature for 30 min. After removal of the solvent, the residue was added with water and ether. The ethereal layer was separated, dried, and evaporated, leaving endo-2'-methyl derivative (Va) as yellow brown oil (680 mg; 85%), bp_2 130—140° (bath temp.). IR (liquid film; cm^{-1}): 2770, 1450, 1313, 1100, 807, 780.

The above amine (Va) was dissolved in ethanol, and methyl iodide added. After stirring for 30 min. and by addition of ether to the solution the methiodide (VIa) was precipitated. Recrystallization from ethanol-tetrahydrofuran afforded yellow plates (VIa), mp 216—219° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}NIFe$: C, 46.85; H, 5.41; N, 3.41. Found: C, 47.20; H, 5.23; N, 3.32.

(b) A solution of the methiodide (IV) (310 mg) in ethanol was catalytically hydrogenated with platinum oxide (40 mg) as catalyst in hydrogen atmosphere. The color of the reaction changed from violet to brown. The reaction mixture was filtrated out of the catalyst, and evaporated. After removal of the solvent, 10% NaOH and ether were added to the brown oil residue. The ethereal layer was separated, washed, dried, and evaporated, leaving as a yellow brown oil (60 mg; 30%), 1',2',5',6'-tetrahydro-N-methyl-*endo*-2'-methylpyrido(3',4')ferrocene (Va). The NMR and IR spectra were indistinguishable with the spectrum described above (a); the methiodide (VIa) was identified through the mp, mixed mp, NMR and IR spectra from the sample of VIa.

1',2',5',6'-Tetrahydro-*exo*-2'-methylpyrido(3',4')ferrocene (Vb)——To a solution of the Grignard reagent (prepared from methyl iodide 0.5 ml and Mg 34 mg) in ether was added 5',6'-dihydropyrido(3',4')ferrocene, and the reaction mixture refluxed for 2 hr. After decomposition with water, the organic layer was separated, dried and evaporated, leaving a yellow brown oil of *exo*-2'-methyl derivative (Vb) (330 mg; 80%), bp_2 125—135° (bath temp.). IR (liquid film; cm^{-1}): 2770, 1450, 1333, 1100, and 810.

It formed a methiodide (VIb) which recrystallized from ethanol, as yellow brown plates, mp 230—235° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}NIFe$: C, 46.85; H, 5.45; N, 3.41. Found: C, 46.92; H, 5.09; N, 3.43.

1',2',5',6'-Tetrahydro-N-methylpyrido(3',4')ferrocene (I)——To a solution of methiodide (VII) (200 mg) in ethanol $NaBH_4$ (100 mg) was added and the reaction mixture stirred at room temperature for 30 min, the color of the reaction mixture changed from violet into pale yellow brown. After removal of the solvent, water and ether were added to the residue. The ethereal layer was separated, dried, and evaporated, leaving a yellow brown oil (86 mg; 80%), 1',2',5',6'-tetrahydro-N-methylpyridoferrocene (I).

The above amine (I) was dissolved in ethanol, and methyl iodide (0.5 ml) added. After stirring for 30 min and addition of ether into the solution methiodide precipitated. Recrystallization from chloroform afforded yellow plates, mp 234—235° (decomp.). *Anal.* Calcd. for $C_{15}H_{20}NIFe$: C, 45.37; H, 5.08; N, 3.53. Found: C, 45.18; H, 5.27; N, 3.45.

1′,2′,5′,6′-Tetrahydro-2′,2′-dimethyl-N-methylpyrido(3′,4′)ferrocene (VIII)——To a solution of the Grignard reagent, which was prepared from methyl iodide (2.0 g) and magnesium (600 mg) in ether, the quaternary salt (IV) (1.12 g) was added, and the reaction mixture refluxed for 2 hr. After decomposition with water, the ether layer was separated and dried. Evaporation of the solvent afforded 2′,2′-dimethyl derivative (VIII) as a yellow brown oil (200 mg; 25%). IR (liquid film; cm^{-1}): 3100, 2950, 1450, 1360, 1105, 1000, and 815.

It formed a methiodide (IX) which recrystallized from ethanol, as a yellow brown plates, mp 172—175° (decomp.). *Anal.* Calcd. for $C_{17}H_{24}NIFe$: C, 48.03; H, 5.69; N, 3.30. Found: C, 48.33; H, 5.88; N, 3.32.

1-Hydroxy-2-aminoethylferrocene (XII)——A solution of 1-hydroxy-1′-cyanomethylferrocene (XI)[5] (4.5 g) in ether was added to a solution of $LiAlH_4$ (2.5 g) in ether, and the reaction mixture refluxed for 1 hr. After decomposition with H_2O, the precipitate was filtered and dried. The filtrate powder was extracted with benzene by refluxing. Golden yellow plates (4.0 g; 80%), mp 166—167°, were obtained from the benzene solution. *Anal.* Calcd. for $C_{12}H_{15}ONFe$: C, 58.14; H, 5.78; N, 5.30. Found: C, 58.81; H, 6.17; N, 5.71.

N-Acetyl-1-hydroxy-2-aminoethylferrocene (XIIIa)——To a mixture of the amino alcohol (XII) (2.45 g) in benzene (50 ml), and NaOH (6 g) in water (60 ml), acetychloride (7.2 ml) was added drop by drop and vigorously stirred for 1 hr at room temperature. After the reaction the benzene layer was separated, washed and dried. Evaporation of the solvent gave a yellow brown solid. Recrystallization from benzene afforded yellow brown plates (1.72 g; 61%), XIIIa mp 128—129°. *Anal.* Calcd. for $C_{14}H_{17}O_2NFe$: C, 58.58; H, 5.99; N, 4.88. Found: C, 58.52; H, 5.77; N, 4.77.

The Bischler–Napieralsky reaction of XIII was carried on under different conditions using several reagents, but unfortunately, we were not successful.

The above recrystallization mother liquid was chromatographed on alumina, and the first elution gave a mixture of the main products together with a crystalline substance, which was recrystallized from benzene and afforded trace of an isomer, mp 209—210°, which was confirmed to be similar to XIIIa according to the spectrum. A second elution gave a solid product as a brown crystalline. This product is assumed to be the diacetyl derivative, which shows bands at 1740, 1650, and 1550 cm^{-1} of the IR spectrum, but it could not be purified because of its decomposition.

N-Benzoyl-1-hydroxy-2-aminoethylferrocene (XIIIb)——Benzoyl chloride (7 ml) was added drop by drop to a mixture of amino alcohol (XII) (1.48 g) in benzene (50 ml), and aqueous NaOH (NaOH 3.54 g in H_2O 5 ml), and vigorously stirred for 5 hr at room temperature. After the reaction the benzene layer was separated, washed, and dried. Removal of the solvents gave a solid as a yellow brown crystalline compound. Recrystallization from EtOH afforded XIIIb, mp 192—193°, as yellow brown plates (1.65 g; 79%). *Anal.* Calcd. for $C_{19}H_{19}O_2NFe$: C, 65.40; H, 5.50; N, 4.01. Found: C, 65.37; H, 5.57; N, 3.94. IR (KBr; cm^{-1}): 3330, 1635, 1540, 1050, 810, and 705.