# **900.** *Ferrocene Derivatives. Part VIII.** *Tetrahydropyridoferrocenes.*

By J. M. OSGERBY and P. L. PAUSON.

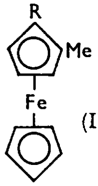
The rearrangement product of (ferrocenylmethyl) trimethylammonium iodide (I) is shown to be dimethyl 2-(ferrocenyl)ethylamine (III). The corresponding primary amine (VIII; R = H) is converted by various routes into di- and tetra-hydropyridoferrocenes.

THE preparation of (ferrocenylmethyl)trimethylammonium iodide (I) was first described by Hauser *et al.*[1] who also studied its rearrangement under the influence of amide ions. This reagent must cause initial hydrogen abstraction, yielding an equilibrium mixture of the zwitterions (IIa) and (IIb), in which the former may be presumed to predominate. These can then undergo a Stevens rearrangement to (IIIa or b), respectively; alternatively the zwitterion (IIb) could rearrange by a cyclic mechanism to the amine (IV; R = $CH_2{\cdot}NMe_2$). The last possibility, while analogous to the "*ortho*-rearrangement" of benzyltrimethylammonium salts, involves a much less favourable transition state for the ferrocene case, where there are two fused five-membered rings.[2] Hauser and his co-workers [3] rejected this, their original formulation (IV; R = $CH_2{\cdot}NMe_2$) for the product, when they observed its Hofmann degradation to vinylferrocene. This evidence is consistent with either structure (IIIa or b), but they were able to eliminate the former by an independent synthesis. That (IIIb) is the structure of the rearrangement product confirms the expectation that the ferrocenylmethyl group, like the benzyl group, would migrate much more readily than methyl, this difference outweighing the effect of the probable position of equilibrium (IIa $\leftrightarrow$ b).

$\text{Fc·CH}_2\text{·NMe}_3^+\ \text{I}^-$ (Fc = ferrocenyl)
(I)

$\text{Fc·}\overset{-}{\text{C}}\text{H·NMe}_3^+$ (a) $\text{Fc·CH}_2\text{·}\overset{+}{\text{N}}\text{Me}_2\text{·CH}_2^-$ (b)
(II)

$\text{Fc·CHMe·NMe}_2$ (a) $\text{Fc·CH}_2\text{·CH}_2\text{·NMe}_2$ (b)
(III)


(IV)

$\text{Fc·CH}_2\text{·CN}$ (V)
$\text{Fc·CH(CN)·NMe}_2$ (VI)
$\text{Fc·CH}_2\text{·CS·NMe}_2$ (VII)
$\text{Fc·CH}_2\text{·CH}_2\text{·NHR}$ (VIII)

However, in deducing structure (IIIb), Hauser *et al.*[3] assigned structure (IV; R = CN) to the product obtained by the action of cyanide ions on the quaternary salt (I). Having proved that this nitrile has the unrearranged structure (V),[4] we reinvestigated the evidence. An alternative synthesis of the tertiary amine (IIIb) appeared desirable, since its structure had been arrived at by a process of elimination. Moreover, its isomer (IIIa) had been synthesised [5] by the reaction of the amino-nitrile (VI) with methylmagnesium iodide, a method which is established in analogous systems [6] but is nevertheless somewhat ambiguous.

Acetylferrocene with sulphur and dimethylamine gave the thioamide (VII), which was reduced in crude form to the amine (IIIb), identical with the rearrangement product. A third method of obtaining this amine, albeit only in the form of its methiodide, was

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* Part VII, Knox and Pauson, *J.*, 1958, 692.

[1] Hauser and Lindsay, *J. Org. Chem.*, 1956, **21**, 382.

[2] Cf. Osgerby and Pauson, *Chem. and Ind.*, 1958, 196.

[3] Hauser, Lindsay, Lednicer, and Cain, *J. Org. Chem.*, 1957, **22**, 717.

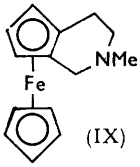
[4] Part VI, Osgerby and Pauson, *J.*, 1958, 656.

[5] Hauser and Lindsay, *J. Org. Chem.*, 1957, **22**, 906.

[6] Stevens *et al.*, *J.*, 1931, 2568; 1932, 2607.

reduction of the cyanide (V) to the primary amine (VIII; R = H) followed by methylation with methyl iodide. The identity of the quaternary salt obtained with that of the rearrangement product was established by comparison of melting points, infrared spectra, and *X*-ray powder diagrams. In the methylation step we avoided the use of formaldehyde–formic acid (the reagent commonly preferred for analogous reactions since it yields the free tertiary amine), realising[2] that it might lead to cyclic products such as (IX). It proved indeed to be this cyclisation which had misled Hauser *et al.*[7] Although at one time they had rejected[7] a cyclic formulation for the formaldehyde–formic acid reaction product, they have recently[8] obtained degradative evidence which supplements and confirms our own synthetic evidence[9] for structure (IX), obtained as follows.

The formation of the cyclic (IX) from the " open " base (VIII; R = H or Me) involves cyclisation of an intermediate of type (X; R = H or Me). It may thus be regarded as an internal aminomethylation analogous to that used to prepare the starting material (I). We therefore first carried out such a process stepwise. Reaction of the primary amine (VIII; R = H) with alkyl sulphates was found to stop at the secondary amine stage. Formaldehyde converted the *N*-methyl derivative (VIII; R = Me) into the methylenebis-derivative (XI) which was then cyclised to the tetrahydropyridoferrocene (IX) identical with a sample obtained[7] from the primary amine (VIII; R = H) in one step with formaldehyde and formic acid.



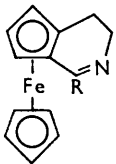
(IX)

$\mathrm{Fc{\cdot}CH_2{\cdot}CH_2{\cdot}NR{\cdot}CH_2^+}$

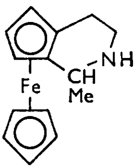
(X)

$\mathrm{(Fc{\cdot}CH_2{\cdot}CH_2{\cdot}NMe)_2CH_2}$

(XI)



(XII)



(XIII)

Alternatively under Bischler–Napieralski conditions *N*-formyl-2-(ferrocenyl)ethylamine (VIII; R = CHO) gave the dihydropyridoferrocene (XII; R = H) which was reduced and methylated to yield the amine (IX), whose methiodide was identical with methiodides of each of the two samples mentioned above.

In the same way the *N*-acetyl derivative (VIII; R = Ac) of the primary amine yielded 1′,2′,5′,6′-tetrahydro-1′-methylpyrido(3′,4′)ferrocene (XIII). Since the methyl group in this compound can be on the same side of the fused ring system as the iron atom, or on the opposite side, two geometrical isomers (each a racemic pair) are possible. However, no separation occurred on chromatography of the product, which yielded a crystalline picrate. Thus a single isomer appears to be obtained under these conditions and an attempt to obtain the second stereoisomer by catalytic hydrogenation (Adams catalyst) (in place of reduction by lithium aluminium hydride) of the intermediate 5′,6′-dihydro-2′-methylpyrido(3′,4′)ferrocene (XII; R = Me) failed. We also failed to dehydrogenate this dihydroisoquinoline analogue (XII; R = Me) with a variety of reagents.

## EXPERIMENTAL

2-(*Ferrocenyl*)*ethylamine* (VIII; R = H).—A solution of ferrocenylacetonitrile[4] (16·5 g., 0·073 mole) in ether was added dropwise during 30 min. to lithium aluminium hydride (6·3 g., 0·17 mole) in ether. The mixture was stirred at room temperature overnight. The excess of hydride was destroyed by addition of moist ether (use of ethyl acetate led to the formation of the *N*-acetyl derivative as a major by-product along with the amine). After later addition of water, the mixture was filtered, the organic layer separated, dried, and evaporated, and the

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[7] Lednicer, Lindsay, and Hauser, *J. Org. Chem.*, 1958, **23**, 653.

[8] Lednicer and Hauser, *J. Org. Chem.*, 1959, **24**, 43.

[9] Osgerby and Pauson, *Chem. and Ind.*, 1958, 1144.

residual oil distilled at 120—125°/0·5 mm., giving 2-(ferrocenyl)ethylamine (13·5 g., 83%) (Found: C, 62·2; H, 6·2; N, 6·1. Calc. for $C_{12}H_{15}FeN$: C, 62·9; H, 6·6; N, 6·1%).

N-*Acetyl*-2-(*ferrocenyl*)*ethylamine* (VIII; R = Ac).—Acetic anhydride (5 ml.) was added to the amine (VIII; R = H) (5·9 g.) in benzene (30 ml.) and the mixture refluxed for ½ hr. under nitrogen, then poured into water. The benzene layer was separated, dried, and evaporated, and the residue recrystallised from cyclohexane. The *acetyl derivative* formed yellow plates, m. p. 117—118° (4·5 g., 65%) (Found: C, 61·9; H, 6·2; N, 4·8. $C_{14}H_{17}FeNO$ requires C, 62·0; H, 6·3; N, 5·2%).

N-*Formyl*-2-(*ferrocenyl*)*ethylamine* (VIII; R = CHO).—To a solution of the amine (VIII; R = H) (11·45 g., 0·05 mole) in ether (200 ml.) was added dropwise a solution of n-butyl-lithium, prepared from lithium (1 g.) and n-butyl bromide (8·56 g.) in ether. After 1 hour's stirring under nitrogen, ethyl formate (5 g., 0·07 mole) in ether (20 ml.) was added and stirring continued overnight. Water was then added and the ether layer separated, dried, and evaporated, yielding the *formyl derivative* (11·1 g., 86%), which crystallised from cyclohexane as yellow plates, m. p. 69—70° (Found: C, 60·7; H, 5·6; N, 5·7. $C_{13}H_{15}FeNO$ requires C, 60·7; H, 5·9; N, 5·5%).

2-(*Ferrocenyl*)*ethyldimethylamine* (IIIb).—(*a*) From the quaternary salt (I) this amine was obtained in 32% yield by following the method of Hauser *et al.*[1,10] It was characterised by its methiodide, m. p. 237° (decomp.) [Hauser *et al.* give figures varying from 240° [7] to 250° (decomp.) [10]], and picrate, m. p. 180—183° (decomp.), greenish-yellow crystals from aqueous ethanol (Hauser *et al.*[10] record m. p. 179—180°).

(*b*) Sulphur (0·67 g.), dimethylamine (25 g.), acetylferrocene (1·86 g.), and dioxan (10 ml.) were heated together in a sealed tube at 130° for 2½ hr. The mixture was evaporated to dryness under reduced pressure and extracted with dioxan. Raney nickel (*ca.* 2 g. suspended in ethanol) was added and the whole heated for 1 hr. on a steam bath. The catalyst was removed and was washed with ethanol and water, and the combined filtrate and washings were concentrated *in vacuo*. The residue was taken up in ether and extracted with dilute hydrochloric acid and the base, liberated by neutralisation of the aqueous layer, was re-extracted into ether. After drying ($Na_2SO_4$) and evaporation, the amine was isolated as its picrate, identical in m. p. and mixed m. p. with the sample described under (*a*). The m. p.s and infrared spectra of the methiodides were likewise identical.

(*c*) A mixture of the amine (VIII; R = H) (0·44 g.), methyl iodide (3·3 ml.), sodium hydrogen carbonate (0·5 g.), and methanol (20 ml.) was refluxed for 60 hr. Water was then added, the solution extracted with chloroform, and the organic layer separated, dried, and evaporated, leaving 2-(ferrocenyl)ethyltrimethylammonium iodide (0·30 g., 40%), m. p. 237°, undepressed on admixture with the methiodide described under (*a*). Identity of these two specimens was confirmed by comparison of infrared spectra and *X*-ray powder diagrams.

The same quaternary salt was obtained (in 61% yield) when the secondary amine (VIII; R = Me) was treated in identical fashion.

2-(*Ferrocenyl*)*ethylmethylamine* (VIII; R = Me).—Sodium (10·3 g., 0·45 g.-atom) was carefully added to a solution of 2-(ferrocenyl)ethylamine (VIII; R = H) (10 g., 0·044 mole) in methanol (300 ml.), followed dropwise by dimethyl sulphate (14 ml., 0·15 mole). The mixture was then refluxed for 4 hr. Solvent was removed *in vacuo*, water added, and the product extracted with benzene. After drying ($Na_2SO_4$) and evaporation of the extract, the dark oily product was chromatographed in benzene on alumina.

2-(*Ferrocenyl*)*ethylmethylamine* (7·03 g., 66%) was obtained as a brown oil, b. p. 96—98°/0·01 mm. (Found: N, 5·7. $C_{13}H_{17}FeN$ requires N, 5·8%). Its *picrate* formed brown plates (from ethanol), m. p. 182—183° (Found: C, 48·1; H, 4·1; N, 11·6. $C_{19}H_{20}FeN_4O_7$ requires C, 48·3; H, 4·3; N, 11·9%).

*NN'*-*Methylene bis*-[2-(*ferrocenyl*)*ethylmethylamine*] (XI).—2-(Ferrocenyl)ethylmethylamine (VIII; R = Me) (6·5 g., 0·027 mole) was dissolved in ethanol (200 ml.), and 30% aqueous formaldehyde (2·5 ml., 0·025 mole) was added. After refluxing for 18 hr., the solvent was removed under reduced pressure, water was added to the residue, and the mixture extracted with benzene. Evaporation of the dried benzene solution left the product (XI), a yellow-brown oil (7·0 g.), characterised as its *picrate*, m. p. 181°, which formed orange rods from aqueous ethanol (Found: C, 49·1; H, 4·3; N, 11·5. $C_{39}H_{40}FeN_8O_{14}$ requires C, 49·0; H, 4·2; N, 11·7%).

3',4'-*Dihydropyrido*(3',4')*ferrocene* (XII; R = H).—To *N*-formyl-2-(ferrocenyl)ethylamine

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[10] Hauser, Lindsay, and Lednicer, *J. Org. Chem.*, 1958, **23**, 358.

(VIII; R = CHO) (5·3 g.) in benzene (50 ml.), phosphorus oxychloride (10 ml.) was added. The mixture was refluxed for 1 hr., then poured on ice, the organic layer removed, and the aqueous layer made alkaline with 2N-sodium hydroxide and extracted with benzene. This extract was dried and concentrated and the product purified by chromatography on alumina with ether as eluent. After removal of the ether *3′,4′-dihydropyrido*(3′,4′)*ferrocene* (XII; R = H) (1·17 g., 50%) distilled at 125—130°/0·03 mm. as a red-brown oil (Found: C, 64·7; H, 5·6; N, 5·9. $C_{13}H_{13}FeN$ requires C, 65·3; H, 5·5; N, 5·9%).

*Tetrahydro*-N-*methylpyrido*(3′,4′)*ferrocene* (IX).—(a) *From* 2-(*ferrocenyl*)*ethylamine* (VIII; R = H).[7] 40% Aqueous formaldehyde (3·4 mol.) was carefully added to a solution of the amine (3·45 g.) in 95% formic acid (0·7 ml.). After the initial reaction had subsided the mixture was heated on a steam bath for 3 hr. The cooled solution was then poured into water, made alkaline with 2N-sodium hydroxide, and extracted with ether. Evaporation, and distillation at 123—125°/0·7 mm., gave the tetrahydro-*N*-methylpyridoferrocene (IX) (2·7 g., 70%) (Found: C, 65·9; H, 6·8; N, 5·4. Calc. for $C_{14}H_{17}FeN$: C, 65·9; H, 6·7; N, 5·5%), characterised by its methiodide,[3,7] m. p. 258° (decomp.) (from $CHCl_3$), and picrate, orange-yellow plates (from aqueous ethanol), m. p. 161° (Found: C, 49·5; H, 4·2; N, 11·1. Calc. for $C_{20}H_{20}FeN_4O_7$: C, 49·6; H, 4·2; N, 11·6%).

(b) *From methylenebis*-[2-(*ferrocenyl*)*ethylmethylamine*] (XI). A solution of this precursor (XI) (7 g.) and phosphoric acid (2 drops; *d* 1·75) in glacial acetic acid (50 ml.) was heated on a water bath for 18 hr., then poured into water and neutralised with 2N-sodium hydroxide. Extraction with ether and removal of the solvent left a dark oil (4·7 g.) which was chromatographed in benzene on alumina. The second of four bands formed yielded tetrahydro-*N*-methylpyrido(3′,4′)ferrocene (IX) (0·6 g., 17%), whose methiodide was indistinguishable in m. p., mixed m. p., and infrared spectrum from the sample described under (a) above.

(c) *From 3′,4′-dihydropyrido*(3′,4′)*ferrocene* (XII; R = H). A solution of this unsaturated cyclic base (0·47 g.) in anisole was added to an excess of lithium aluminium hydride in anisole. The mixture was stirred at room temperature under nitrogen for 3 hr. and the excess of hydride then destroyed by moist ether followed by water. The product was extracted from the organic phase with 2N-hydrochloric acid, liberated with 2N-sodium hydroxide, and then re-extracted into benzene. Removal of this solvent left the tetrahydropyridoferrocene (0·24 g.) which was not purified but was dissolved in methanol containing sodium methoxide and treated with an excess of dimethyl sulphate. The mixture was refluxed for 1 hr., cooled, and treated with water. Extraction of the resultant tetrahydro-*N*-methylpyridoferrocene with ether followed by addition of methyl iodide to the ether solution precipitated the methiodide, identical in m. p., mixed m. p., and infrared spectrum with the samples described under (a) and (b).

*3′,4′-Dihydro-1′-methylpyrido*(3′,4′)*ferrocene* (XII; R = Me).—To *N*-acetyl-2-(ferrocenyl)-ethylamine (VIII; R = Ac) (3·9 g., 0·014 mole) in dry benzene (60 ml.), phosphorus oxychloride (20 ml.) was added, and the mixture then refluxed. After a few minutes a deep-purple colour was observed. After 1 hr. the solution was poured into water and the colourless benzene solution separated from the purple aqueous layer. Neutralisation of the latter with 2N-potassium hydroxide discharged this colour and liberated the yellow product, which was extracted into benzene. Removal of the solvent under reduced pressure left a yellow-brown oil (3·1 g., 85%), b. p. 115—120°/0·05 mm., which was chromatographed on alumina and redistilled. The *3′,4′-dihydro-1′-methylpyrido*(3′,4′)*ferrocene* (XII; R = Me) so obtained solidified but could not be recrystallised (Found: C, 66·3; H, 6·0; N, 5·5, 5·6. $C_{14}H_{15}FeN$ requires C, 66·4; H, 5·9; N, 5·5%). It formed a *picrate* which, crystallised from acetone, had m. p. 214° (decomp.) (Found: C, 49·6; H, 4·2; N, 11·8. $C_{20}H_{18}FeN_4O_7$ requires C, 49·8; H, 3·8; N, 11·6%), and a *methiodide*, m. p. 203—204° (decomp.) (Found: C, 45·9; H, 5·0; N, 3·8. $C_{15}H_{18}FeIN$ requires C, 45·6; H, 4·6; N, 3·55%).

*1′,2′,5′,6′-Tetrahydro-1′-methylpyrido*(3′,4′)*ferrocene*.—3′,4′-Dihydro-1′-methylpyrido-(3′,4′)ferrocene (XII; R = Me) (1 g.) in ether was added to an excess of ethereal lithium aluminium hydride, and the mixture stirred at room temperature for 2 hr. Wet ether was then added, followed by water. The organic layer was separated, dried, and evaporated, leaving a yellow oil (0·85 g., 84%). This was chromatographed in benzene on alumina. Ether slowly eluted a single yellow band. Addition of picric acid to the eluate afforded the *tetrahydromethylpyrido*(3′,4′)*ferrocene picrate*, which crystallised from aqueous acetone as yellow plates, m. p. 196° (decomp.) (Found: C, 49·4; H, 4·35; N, 11·4. $C_{20}H_{20}FeN_4O_7$ requires C, 49·6; H, 4·2; N, 11·6%).

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THE UNIVERSITY, SHEFFIELD, 10.
[Present address (P. L. P.): THE ROYAL COLLEGE OF SCIENCE AND TECHNOLOGY,
GLASGOW.]

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