

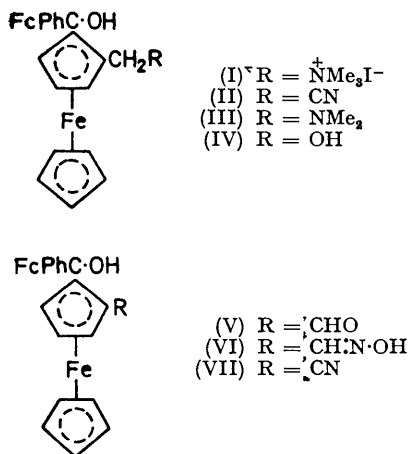
Unsymmetrically Disubstituted Ferrocenes. Part XIII.^{1,2} Neighbouring Group Participation in the Conversion of 2-Substituted Ferrocenylacetonitriles into Ferrocenylacetamides

By J. H. Peet and B. W. Rockett,* The Department of Physical Sciences, The Polytechnic, Wolverhampton WV1 1LY

In the presence of cyanide ion, substituted 1-cyanomethyl-2-hydroxymethylferrocenes were converted into the corresponding amides while at the same time the hydroxy-group was displaced by cyanide. The effect of solvent and substituent groups on this reaction has been studied and evidence for participation by the neighbouring hydroxy-group in the conversion of the cyanide into the amide is presented.

PARTICIPATION by neighbouring *ortho*-groups has been proposed to account for unexpected features in the reactions of numerous benzene derivatives.³ We report the first observation of this effect in the chemistry of 1,2-disubstituted ferrocenes.

The methiodide (I) was characterized as a mixture of two diastereoisomers, as expected for a structure containing an asymmetric carbon atom.⁴ On treatment with aqueous potassium cyanide each isomer gave the corresponding nitrile (II) as the only product. However in aqueous ethanolic potassium cyanide each isomer gave only the corresponding amide (XV). When the diastereoisomeric nitriles (II) were heated to reflux with aqueous ethanolic potassium cyanide then the corresponding amide (XV) was formed in each case, and these



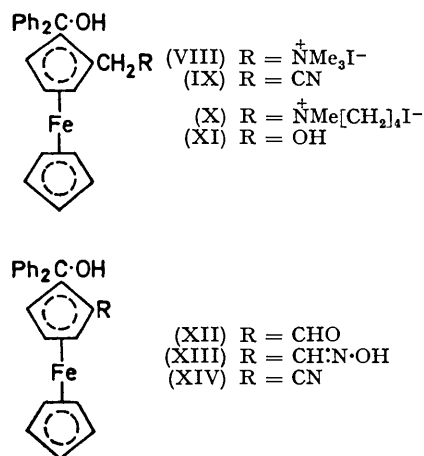
products were identical with those obtained in the previous reaction. The methiodide (VIII) gave, in the same way, the nitrile (IX) with aqueous cyanide and the amide (XVI) when aqueous ethanol was the solvent. The same amide was formed from the nitrile (IX) with aqueous ethanolic cyanide. When the trimethylammonium leaving group in the methiodide (VIII) was replaced by the *N*-methylpyrrolidinyll group (X) then the reagents and conditions required to form the nitrile (IX) and the amide (XVI) were unchanged.

The source of the cyanide group in the conversion of the nitrile (IX) into the amide (XVI) was shown to be

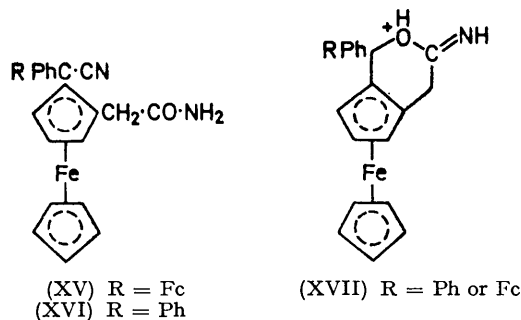
¹ Part XII, D. R. Morris and B. W. Rockett, *J. Organometallic Chem.*, 1972, **35**, 179.

² Preliminary communication, J. H. J. Peet and B. W. Rockett, *Chem. Comm.*, 1968, 120.

inorganic by the incorporation of ¹⁴CN into the amide (XVI) when the nitrile (IX) was treated with aqueous



ethanolic K¹⁴CN. Similar levels of radioactivity were obtained when the methiodide (VIII) was converted into the labelled nitrile with aqueous K¹⁴CN and then into the amide. Both ferrocenylmethyl cyanide and the diols (IV) and (XI) were inert towards aqueous ethanolic potassium cyanide, nor did they take up radioactivity from K¹⁴CN in aqueous ethanol. It was shown that the



hydroxy-group of the nitrile (IX) was involved in the conversion of the cyanide group into the amide group by carrying out the reaction in dried ethanol and in dried nitrobenzene. In each solvent the nitrile (IX) was converted smoothly into the amide (XVI). These results are consistent with a mechanism where the

³ E. S. Gould, 'Mechanism and Structure in Organic Chemistry,' Holt, Rinehart and Winston, New York, 1960, p. 561.

⁴ E. A. Hill and J. H. Richards, *J. Amer. Chem. Soc.*, 1961, **83**, 4216.

hydrolysis of the nitriles (VII) and (IX) is assisted by intramolecular addition of the hydroxy-group to the carbon-nitrogen triple bond. This is followed by attack with cyanide ion on the diaryl-substituted carbon atom in the intermediate oxonium species (XVII).

The nature of the products obtained on reduction of *o*-nitrobenzonitriles has been shown to depend critically on the reaction conditions, and participation by the neighbouring nitro-group in the formation of *o*-nitrobenzamide has been suggested.⁵

The methiodides (VIII) and (X) were prepared as described previously,^{6,7} and the methiodides (I) were obtained by treatment of 1-dimethylaminomethyl-2-lithioferrocene⁴ with benzoylferrocene, separation of the diastereoisomeric products (III) by chromatography, and quaternisation of each with methyl iodide. The amines (III) showed intramolecular N...H-O hydrogen bonding⁶ and the differences in their n.m.r. spectra allowed the tentative assignment of the relative structures (see Experimental section). Hydrolysis of the methiodides (I) proceeded normally to give the diols (IV). The rates of hydrolysis were enhanced more than twenty-fold over the rate for the methiodide (VIII), and this was attributed to inductive electron release by the ferrocenyl substituent in each of the methiodides (I). The diols (IV) and (XI) were oxidized smoothly with manganese dioxide to the aldehydes (V) and (XII), which were characterised as the oximes (VI) and (XIII) and converted into the nitriles (VII) and (XIV). The aldehyde (XII)⁷ was also obtained from the methiodide (VIII) under Sommelet conditions and disproportionated to the diol (XI) when subjected to the Cannizzaro reaction.

EXPERIMENTAL

For general directions see Part I.⁸

The methiodide (VIII), nitrile (IX), and diol (XI) were prepared according to reported methods.⁶ The pyrrolidine derivative (X) was obtained as previously described.⁸

1-(Dimethylaminomethyl)-2-(α -ferrocenyl- α -hydroxybenzyl)-ferrocene (III).—1-(Dimethylaminomethyl)-2-lithioferrocene⁴ (0.06 mol) was prepared in dry ether solution and benzoylferrocene (26.1 g, 0.09 mol) was added as a slurry in ether; the mixture was stirred at room temperature for 2 h, hydrolysed with a little water, acidified with phosphoric acid, and extracted with ether to remove the excess of benzoylferrocene. After neutralization with sodium hydrogen carbonate, the aqueous layer was extracted with ether and chromatographed on alumina. Benzene eluted one isomer (a) of the amine (III) and ether eluted the second isomer (b). The total yield of the diastereoisomers was 12.2 g (32%). Crystallization from ethanol gave orange crystals of *isomer* (a), m.p. 146–147° (Found: C, 67.4; H, 5.9; N, 2.4. C₃₀H₃₁Fe₂NO requires C, 67.4; H, 5.85; N, 2.6%). *Isomer* (b) had m.p. 165–166° (Found: C, 67.7; H, 5.8; N, 2.3%).

The amines (III) were converted into the orange methiod-

⁵ P. Grammaticakis, *Bull. Soc. chim. France*, 1953, 207; K. Butler and M. W. Partridge, *J. Chem. Soc.*, 1959, 2396; H. Musso and H. Schroder, *Chem. Ber.*, 1965, **98**, 1562.

⁶ D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Amer. Chem. Soc.*, 1965, **87**, 1241.

ides (I). *Methiodide* (Ia) from isomer (a), crystallized from acetonitrile-ether, had m.p. 160° (decomp.) (Found: C, 55.3; H, 5.2; Fe, 16.4; C₃₁H₃₄Fe₂INO requires C, 55.15; H, 5.1; Fe, 16.55%). *Methiodide* (Ib) from isomer (b) crystallized as an acetonitrile solvate, m.p. 190° (decomp.) (Found: C, 55.0; H, 4.85; N, 3.2; C₃₁H₃₄Fe₂INO.0.5-CH₃CN requires C, 55.25; H, 5.15; N, 3.0%).

¹H N.m.r. absorptions: (IIIa) τ 7.88 (6H, s, NMe₂), 7.58(d) and 6.55(d) (2H, *J* 12 Hz, CH₂), 6.12(s) and 6.10(s) (2 \times C₅H₅), 6.02 (3H, m, C₅H₃), 5.89 (4H, m, C₅H₄), and 2.59 (5H, m, Ph); (IIIb), 8.02 (6H, s, NMe₂), 7.48(d) and 6.73(d) (2H, *J* 14 Hz, CH₂), 6.01(s) and 5.86(s) (2 \times C₅H₅), 6.03 (3H, m, C₅H₃), 5.88 (4H, m, C₅H₄), and 2.60 (5H, m, Ph).

1-Cyanomethyl-2-(α -ferrocenyl- α -hydroxybenzyl)ferrocene (II).—The methiodide (Ib) (1.0 g, 1.5 mmol) was treated with potassium cyanide (3.5 g) in water (100 ml) under reflux for 24 h. Extraction with ether gave the yellow nitrile (II) (0.40 g, 87% based on recovered methiodide), m.p. 217–219° (from benzene-petroleum) (Found: C, 67.4; H, 5.0; Fe, 21.8. C₂₈H₂₅Fe₂NO requires C, 67.5; H, 5.1; Fe, 21.65%).

The methiodide (Ia) similarly gave (quantitatively) the nitrile (IIa) as orange plates, m.p. 157–158° (Found: N, 2.5. C₂₈H₂₅Fe₂NO requires N, 2.5%).

2-(α -Cyano- α -ferrocenylbenzyl)ferrocen-1-ylacetamide (XV).—The methiodide (Ib) (0.7 g, 1.05 mmol), potassium cyanide (2.4 g), and 1:1 water-ethanol (50 ml) were heated together under reflux for 24 h and then extracted with ether. The yellow amide (XVb) (0.25 g, 71%), crystallized from benzene-petroleum, had m.p. 239–240° (Found: C, 66.8; H, 4.6; Fe, 20.3; N, 5.0. C₃₀H₂₆Fe₂N₂O requires C, 66.45; H, 4.8; Fe, 20.6; N, 5.2%).

The amide (XVa) was obtained from methiodide (Ia) in the same way in 63% yield as a brown powder, m.p. 192–194° (from benzene) (Found: C, 66.4; H, 4.9; N, 4.8%).

2-[Cyano(diphenyl)methyl]ferrocen-1-ylacetamide (XVI).—The methiodide (VIII) was treated with aqueous ethanolic potassium cyanide as in the preparation of the amides (II). The amide (XVI) (69% yield) had m.p. 235.5–237° (ethanol) (Found: C, 72.15; H, 5.2; Fe, 12.5; N, 6.6. C₂₆H₂₂FeN₂O requires C, 71.9; H, 5.1; Fe, 12.9; N, 6.5%).

The amide (XVI) was also obtained (57% yield) by treatment of the nitrile (IX) with ethanolic potassium cyanide. The pyrrolidine methiodide (X) gave a 36% yield of the amide under similar conditions. The nitrile (IX) was converted into the amide (XVI) in anhydrous nitrobenzene (9% yield) and in anhydrous ethanol (37% yield).

Displacements with K¹⁴CN.—The reaction of the methiodide (VIII) with aqueous potassium cyanide⁶ was repeated in the presence of radioactive potassium cyanide. A sample of the nitrile (IX) was retained for activity determination, and the rest was treated with inactive potassium cyanide in aqueous ethanol and the amide (XVI) was isolated. Similar molar activities were found for the nitrile (IX) and the amide (XVI).

In a similar manner, the inactive nitrile (IX) was heated under reflux with aqueous ethanolic labelled potassium cyanide. The amide (XVI) had a molar activity similar to that observed in the first experiment.

⁷ G. Marr, J. H. J. Peet, B. W. Rockett, and A. Rushworth, *J. Organometallic Chem.*, 1967, **8**, P17.

⁸ M. Haddington, B. W. Rockett, and A. Nelhans, *J. Chem. Soc. (C)*, 1967, 1436.

When ferrocenylmethyl cyanide was heated under reflux with active cyanide in aqueous ethanolic solution, the isolated nitrile was radioinactive.

1-Hydroxymethyl-2-(α -ferrocenyl- α -hydroxybenzyl)ferrocene (IV).—The methiodide (Ia) (2.0 g, 3 mmol) was heated to reflux with m-sodium hydroxide solution (200 ml) for 24 h. The cooled product was extracted with ether and chromatographed on alumina. Benzene-ether eluted *bis*-[2-(α -ferrocenyl- α -hydroxybenzyl)ferrocen-1-ylmethyl] ether (0.34 g, 23%) which crystallized from benzene-petroleum as a yellow solid, m.p. 210° (decomp.) (Found: C, 68.2; H, 5.1; Fe, 22.2. $C_{26}H_{50}Fe_4O_3$ requires C, 67.6; H, 5.1; Fe, 22.5%).

Ether containing 1% methanol eluted the yellow diol (IVa) (0.8 g, 53%), m.p. 144–145° (from petroleum) (Found: C, 66.6; H, 5.2; Fe, 21.8. $C_{28}H_{28}Fe_2O_2$ requires C, 66.4; H, 5.2; Fe, 22.1%).

The methiodide (Ib) similarly gave the diol (IVb) (93%), m.p. 162–163° (Found: C, 66.1; H, 5.35%).

2-(α -Ferrocenyl- α -hydroxybenzyl)ferrocene-1-carbaldehyde (V).—The diol (IVb) (0.5 g, 1 mmol) dissolved in chloroform (20 ml) was stirred with 'active' manganese dioxide (2.5 g) for 2 days. The mixture was filtered and the solution chromatographed. Ether eluted the aldehyde (Vb), a red solid (0.25 g, 50%), m.p. 190–191° (from ethanol) (Found: C, 66.7; H, 4.8; Fe, 22.2. $C_{28}H_{24}Fe_2O_2$ requires C, 66.7; H, 4.8; Fe, 22.2%).

The aldehyde (Vb) was converted to the orange oxime (VIb), which crystallized from benzene-petroleum as a benzene solvate m.p. 225° (Found: Fe, 19.4. $C_{28}H_{25}Fe_2NO_2 \cdot C_6H_6$ requires Fe, 19.1%).

2-(α -Ferrocenyl- α -hydroxybenzyl)ferrocene-1-carbonitrile (VII).—The oxime (VIb) (0.6 g, 1.2 mmol) and dicyclohexylcarbodi-imide (1.1 g) were dissolved in dry benzene and heated under reflux for 1 day. The product was chromatographed; ether eluted the yellow product (0.24 g, 48%), m.p. 230° (decomp.) (from ethanol) (Found: C, 66.4;

H, 4.6; Fe, 22.0. $C_{26}H_{23}Fe_2NO$ requires C, 67.1; H, 4.6; Fe, 22.3%).

2-[Hydroxy(diphenyl)methyl]ferrocene-1-carbaldehyde (XII).—The methiodide (VIII) was treated with manganese dioxide as already described. The aldehyde (XII) was eluted from alumina with benzene (yield 3.75 g, 75%); m.p. 235–236° (from ethanol); oxime (XIII) m.p. 206.5–208° (from ethanol) (Found: C, 70.2; H, 5.1; Fe, 13.4. $C_{24}H_{21}FeNO_2$ requires C, 70.1; H, 5.15%; Fe, 13.6%); barbiturate (prepared in acetic acid), m.p. >270° (from benzene-petroleum) (Found: C, 64.0; H, 4.3; Fe, 10.9. $C_{27}H_{22}FeN_3O_4$ requires C, 63.8; H, 4.4; Fe, 11.0%).

When the methiodide (VIII) (9.0 g, 16 mmol) was treated with acetic acid (150 ml) and hexamine (12.0 g, 84 mmol) and boiled for 15 min, the aldehyde (XII) was obtained (2.5 g, 38%).

Cannizzaro Reaction of the Aldehyde (XII).—The aldehyde (XII) (0.7 g, 0.18 mmol), potassium hydroxide (10 g), ethanol (13 ml), water (7 ml), and silver catalyst⁹ (0.3 g) were heated together at 60° for 2 days. The ether extract of the product was chromatographed on alumina to give unchanged aldehyde (0.1 g) and 2-[hydroxy(diphenyl)methyl]ferrocen-1-ylmethanol (XI) (0.22 g, 37%), as shown by m.p. and i.r. spectrum.

2-[Hydroxy(diphenyl)methyl]ferrocene-1-carbonitrile (XIV).—The oxime (XIII) (0.65 g) was dehydrated with dicyclohexylcarbodi-imide as already described to give the yellow nitrile (XIV) (0.37 g, 60%), m.p. 196–198° (from ethanol) (Found: C, 72.6; H, 4.8. $C_{24}H_{19}FeNO$ requires C, 73.3; H, 4.9%).

We thank Dr. G. Marr for discussions.

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⁹ R. A. Khalibullina, L. G. Fatulina, and Kh. R. Rustamov, *Uzbek. khim. Zhur.*, 1966, 54.