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NEW METALLOCENIC PHENYLALANINE ANALOGS

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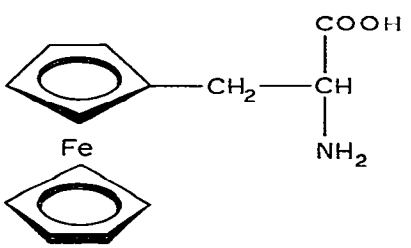
Summary

The syntheses of two new metallocenic analogues of phenylalanine: D,L-β-cymantrenyl alanine and D,L-β-tricarbonyl(cyclobutadienylalanine)iron are described.

Introduction

D,L-ferrocenyl alanine (Fer), I, the ferrocene analogue of phenylalanine, was synthesized by Osgerby and Pauson [1] using the formamido malonate route.



(I)

Recently, Hanzlick et al. [2] studied the interaction of I with phenylalanine hydroxylase and phenylalanine decarboxylase. They found that in those systems, I behaved like other classical analogues of phenylalanine. These observations and previous results indicating that ferrocene is metabolized in rats by aromatic hydroxylation and conjugation with glucuronic acid [3] clearly show that ferrocene can behave as a simple benzene analogue in biological systems.

It has also been shown that I can be incorporated in peptides. Blaha et al.

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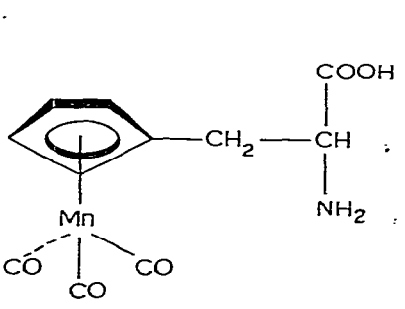
[4] separated the two enantiomers of I and used standard solution methods to make the two diastereoisomeric diketopiperazines: cyclo L-Pro-L-Fer and cyclo L-Pro-D-Fer. By solid phase methods, we were able to incorporate I into medium-sized biologically active peptides (enkephalin [5], bradykinin and substance P [6]). In those cases, we used the elongated aromatic system of ferrocene as a steric probe to study peptide receptor interactions.

Furthermore, there has been a renewal of interest in the biological importance of so-called "super aromatic" amino acids analogs: carboranylalanine (Car) and Car-containing peptides have been extensively studied [7]; naphthylalanine has been claimed to be an effective sleep inducer in animals [8]. New metallocenic amino acids are appropriate species for extending these studies and they can also provide a new class of biologically useful photoaffinity and or radioactive labels.

Results and discussion

In order to extend these studies, we have synthesized two other metallocenic amino acids: cymantrenyl alanine (Cym) II and tricarbonyl (cyclobutadienyl-alanine)iron (Cyc) III. Cym and Cyc like Fer possess aromatic character in the



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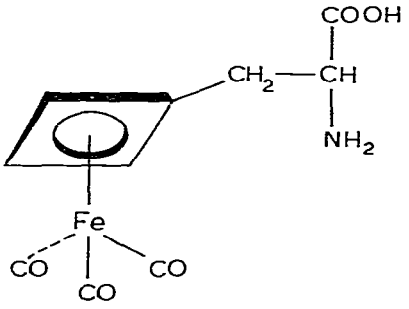


(III)

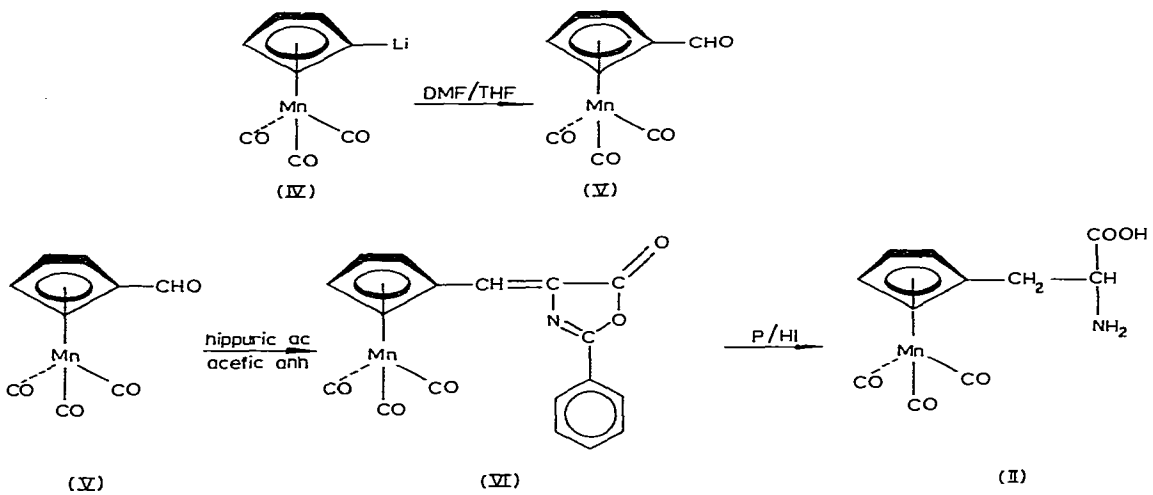
metallocenic moiety, but they differ from Fer in the unsymmetrical environments of their metal atoms.

It must be emphasized that under irradiation their carbonyl ligands can be easily replaced by various species such as amines, and this could be useful for photoaffinity labelling of biological molecules.

Synthesis of cymantrenyl alanine II

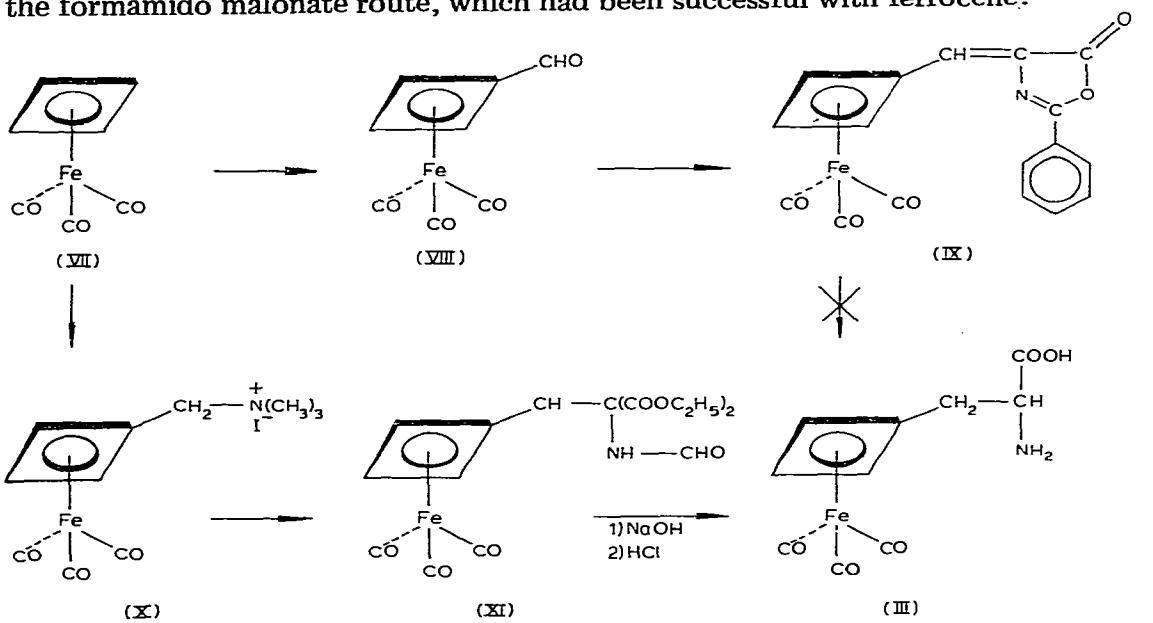
Due to the fact that methylation of the amino group fails with cymantrene, the formamidomalonate route was not practicable. II was thus prepared from the azlactone as follows *: formyl cymantrene V was prepared by reaction in THF at low temperature between cymantrenyl IV and dimethyl formamide [9]. Compound V was then treated with hippuric acid to yield the azlactone VI. Reduction of VI using phosphorus and hydriodic acid in acetic anhydride gave II in 60% overall yield.

* Osgerby and Pauson tried without success to use the azlactone route with ferrocene [1].



Synthesis of tricarbonyl(cyclobutadienylalanine)iron III

We first tried the azlactone route with cyclobutadieneiron tricarbonyl VII, which was first formylated by the Vilsmeier reaction [10]. Condensation with hippuric acid converted the formylated derivative VIII into the azlactone IX; but IX was unstable under the reduction conditions we used. Thus we turned to the formamido malonate route, which had been successful with ferrocene:



VII was converted into the trimethylammonium iodide derivative X by treatment with methylenebisdimethyl amine in glacial acetic acid VIII. The salt X was then converted into XI by treatment with diethylsodioformamido malonate. The ester XI was hydrolysed and decarboxylated to give III in 30% overall yield *.

* Loss in the first step (VII → X) mainly accounts for this low yield, as the subsequent steps (X → XI and XI → III) give almost quantitative yields and are surprisingly fast (about hundred times faster than with the ferrocene derivatives).

Experimental

Azlactone, VI

Cymantrenyl carboxaldehyde V (1.09 g; 4.7 meq.), hippuric acid (1 g; 5.6 meq), and freshly fused sodium acetate (0.4 g; 5 mmol) were dissolved in refluxing acetic anhydride (5 ml), stirring in a stream of nitrogen until the mixture became liquid and red. The solution was then refluxed for a further 2 hours under nitrogen and methanol (6 ml) was then slowly added. The mixture was kept in the refrigerate or overnight then the yellow crystals were filtered off, washed with ice-cold methanol, and dried (1.2 g; 70%; m.p. 176°C).

Cymantrenyl alanine: Cym II

Hydriodic acid (4 ml) were added under nitrogen during 1 h to a stirred mixture of azlactone VI (1 g; 2.7 meq) and red phosphorus (0.54 g) in acetic anhydride (8 ml). The mixture was refluxed for 3 to 4 hours, then cooled, and filtered, The unreacted phosphorus on the filter was washed with glacial acetic acid. The filtrate and washings were evaporated to dryness under reduced pressure, then water (40 ml) was added and the solution was neutralized with 15 per cent aqueous ammonia. The cymantrenyl alanine II separated in pale yellow plates which were filtered off and dried (0.80 g; 90%; m.p. 230°C). IR (KBr, cm^{-1}): 3200, 2000—1950 (carbonyl), 1600, 1400, 1320, 670, 630. Mass spectrum: 292 (M^+), 276, 246. Found: C, 44.91; H, 3.44; Mn, 19.15; N, 4.75. $C_{11}H_{10}MnNO_5$ (292) calcd.: C, 45.38; H, 3.46; Mn, 18.87; N, 4.81%.

Tricarbonyl[(cyclobutadienylmethyl)formamidomalonate]iron, XI

The quaternary salt X (3 g; 7.71 mmol) was added to a solution of diethylsodioformamidomalonate, prepared by dissolving first sodium (0.35 g; 15.4 mmol) and then diethyl formamidomalonate (3.11 g; 15.4 mmol) in anhydrous ethanol (60 ml). The mixture was refluxed and stirred for 15 minutes in a slow current of nitrogen. It was then filtered, and the solvent removed under reduced pressure. After addition of water to the residue, the mixture was extracted twice with ether, and the ether solution was washed twice with water, then dried, and evaporated to leave an oil, which later crystallised. Recrystallisation from 60/40 ethanol/water gave the pure product (2 g; 94%; m.p. 108—109°C). IR (KBr, cm^{-1}): 2030—1950 (carbonyl), 1740 (ester), 1655 (aldehyde), 610, 580, 500 (Fe—C—O).

Azlactone, IX

Tricarbonyl(cyclobutadienecarboxaldehyde)iron, VIII (2.15 g; 0.98×10^{-2} mol), hippuric acid (1.92 g; 1.07×10^{-2} mol) and anhydrous sodium acetate (0.8 g; 0.98×10^{-2} mol) were dissolved during 5 min in refluxing acetic anhydride (5 ml), in a stream of nitrogen. The solution was heated for 1.5 hour on a steam bath, then cooled, diluted with ethanol (6 ml), and kept in the refrigerate of overnight. The product was filtered off then recrystallised from benzene/alcohol to give the pure azlactone IX (3 g; 85%) as deep orange crystals, m.p. 175—176°C. IR (KBr, cm^{-1}): 2050, 1980, 1960 (carbonyl), 1780, 1750 (C=N, C=O), 1640 (C=C), 600, 580, 511 (Fe—C—O). ^1H NMR (δ, ppm, CD_3COCD_3, TMS): 8.30 (m, 2 H), 7.80 (m, 3 H) (C_6H_5), 6.88 (s, 1 H) (—CH=),

5.2 (s, 2 H), 4.5 (s, 1 H) (cyclobutadiene). Mass spectrum: 363 (M^+), 335, 307, 279.

Tricarbonyl(cyclobutadienylalanine)iron, Cyc III

The ester XI (1 g) was refluxed for 15 minutes with a solution of sodium hydroxyde (1 g) in water (7 ml) and ethanol (9 ml) in a slow current of nitrogen. The mixture was then filtered and evaporated to dryness under reduced pressure. After addition of 2 *N* HCl (30 ml) the mixture was refluxed and stirred for 15 minutes under nitrogen and concentrated under reduced pressure until the hydrochloride began to precipitate, and the pH was then adjusted to 7 with 40% sodium hydroxide. The solvent was evaporated to dryness under reduced pressure, and recrystallisation of the residue from ethanol gave pale yellow crystals (600 mg; 75%; m.p. 220°C (decomp.)). Found: C, 41.47; H, 3.80; N, 4.69; Fe, 19.23. $C_{10}H_9FeNO_5$ calcd.: C, 40.40; H, 3.70; N, 4.71; Fe, 18.85. IR (KBr, cm^{-1}): 2080, 1950 (carbonyl), 1600, 1520, 1420, 1390, 1320, 1310, 610, 580, 560. Mass spectrum: 251, 223, 195, 149, 123.

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