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Studies on Ferrocene and Its Derivatives. I. Reactions of Formylferrocene with α-Amino Acids

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Synopsis. The condensation reactions of formylferrocene (I) with various α-amino acids and their esters were studied. The products are new Schiff bases (II) which may be of medicinal value.

From a medicinal point of view, ferrocene is considered to be potent for treatment of iron deficiency anaemia.[1,2] However, it needs to be prepared in the form of a suitable derivative.

The present investigation is an attempt to prepare some new derivatives of ferrocene, likely to be used as haematinics, by interaction of formylferrocene (I) with α-amino acids or their esters. The reaction proceeded smoothly in ethanol and in the presence of sodium carbonate to give quantitative yields of the Schiff bases (II). The time of reaction and purity of the products were controlled by thin layer chromatography (tlc):

$$\underset{\text{(I)}}{\text{Fc–CHO} + \text{H}_2\text{N–CH(COOR')–R}} \xrightarrow[\text{Na}_2\text{CO}_3]{\text{EtOH}} \underset{\text{(II)}}{\text{Fc–CH=N–CH(COOR')–R}}$$

(Fc=ferrocenyl; R=alkyl and others; R'=H or ethyl)

The prepared Schiff bases are brown crystals, sparingly soluble in hot water, easily soluble in ethanol and alkali solution, and insoluble in most organic solvents. They are easily hydrolyzed by dilute acids to their original components. Compounds (II) are likely to inherit the properties of the reactant entities and possess some new medicinal properties.

The results of the above reactions are given in Table 1.

Experimental

General Method of Preparation of Schiff Bases (II). An equimolecular mixture of formylferrocene (I) and an α-amino acid or its ester was refluxed for about two hours in absolute ethanol in the presence of 2 mol of anhydrous sodium carbonate. The reaction mixture was filtered while hot, whereby the Schiff base precipitated after concentration as a brown solid. In certain cases, addition of a few drops of absolute ether is necessary to precipitate the reaction product. The time of reaction and purity of the products were controlled by thin-layer chromatography. Purification of the Schiff bases was effected by dissolution in a minimum volume of absolute ethanol, and precipitation with absolute ether. The results are presented in Table 1: melting points were uncorrected, and the solvent used for tlc estimation of R_f value was a 20: 1 benzene–ethanol mixture.

Hydrolysis of Schiff Bases (II). A sample of the Schiff base (II; R=H, R'=Et) was covered with 2 M HCl, then heated for about half an hour. The reaction mixture was filtered while hot, whereby formylferrocene (I) was isolated as dark brown crystals (mp 223—224 °C). It was identified by means of the mixed melting point test with an authentic sample, and by the identical R_f value (0.26, benzene). The filtrate from the reaction mixture was concentrated and cooled to precipitate the amino acid hydrochloride, which on neutralisation deposited the free amino acid (identified by mp and R_f value).

References

1) British Pat. 819108, 26.8.59. (Imperial Chemical Industries, Ltd.)
2) British Pat. 869504, 31.5.61; 870949, 21.6.61. (Imperial Chemical Industries, Ltd.).

TABLE 1. Fc–CH=N–R″

Amino acid part (=N–R″)	Yield	Mp (°C)	R_f	Molecular formula	Obsd (%)			Calcd (%)		
					C	H	N	C	H	N
Glycine	92	270	0.65	$C_{13}H_{13}O_2NFe$	57.23	4.69	5.11	57.38	4.8	5.16
DL-Alanine	90	200—201	0.57	$C_{14}H_{15}O_2NFe$	58.85	5.19	4.90	58.93	5.26	4.91
β-Alanine	88	213—214	0.55	$C_{14}H_{15}O_2NFe$	58.84	5.15	4.90	58.94	5.26	4.91
DL-Valine	93	215	0.73	$C_{16}H_{19}O_2NFe$	61.17	5.93	4.45	61.32	6.07	4.47
DL-Leucine	90	204—205	0.64	$C_{17}H_{21}O_2NFe$	62.28	6.35	4.28	62.39	6.42	4.28
DL-Isoleucine	87	250	0.80	$C_{17}H_{21}O_2NFe$	62.25	6.40	4.29	62.39	6.42	4.28
L-Glutamic acid	95	265—267	0.63	$C_{16}H_{17}O_4NFe$	55.88	4.87	3.99	55.97	4.95	4.08
DL-Aspartic acid	95	232—233	0.59	$C_{15}H_{15}O_4NFe$	54.60	4.46	4.22	54.71	4.55	4.26
L-Tyrosine	90	230	0.72	$C_{20}H_{19}O_4NFe$	60.95	4.47	3.48	61.06	4.83	3.56
DL-Tyrosine	88	190—191	0.64	$C_{22}H_{20}O_2NFe$	52.71	3.92	5.67	52.80	4.00	5.60
L-Methionine	87	229—230	0.71	$C_{16}H_{19}O_2NSFe$	55.54	5.39	3.98	55.65	5.50	4.06
L-Cystine	88	260—261	0.61	$C_{28}H_{28}N_2O_4S_2Fe_2$	53.02	4.31	4.35	53.16	4.43	4.43
L-Arginine	87	238—239	0.51	$C_{28}H_{30}N_3O_2Fe$	59.23	5.19	9.81	59.36	5.30	9.89
Glycine ethyl ester	90	140	0.61	$C_{16}H_{17}O_2NFe$	59.89	5.51	4.63	60.02	5.69	4.70
DL-Alanine ethyl ester	89	173	0.63	$C_{16}H_{19}O_2NFe$	61.15	5.93	4.38	61.32	6.07	4.47
DL-Valine ethyl ester	91	230	0.65	$C_{18}H_{23}O_2NFe$	63.21	6.66	3.99	63.34	6.74	4.10
L-Leucine ethyl ester	90	291—292	0.62	$C_{19}H_{25}O_2NFe$	64.08	6.91	3.82	64.22	7.04	3.94

Fc=Ferrocenyl