

CCA-613

547.559.07

Original Scientific Paper

## Ferrocene Compounds. I. Acetylferrocene and Diethyl Oxalate Condensation Products and Their Derivatives

M. Laćan and V. Rapić

Laboratory of Organic Chemistry and Technology, Biochemistry Department, Faculty of Technology, University of Zagreb and Laboratory of Organic Synthesis, Institute of Food Science and Technology, Zagreb, Croatia, Yugoslavia

Received January 30, 1970

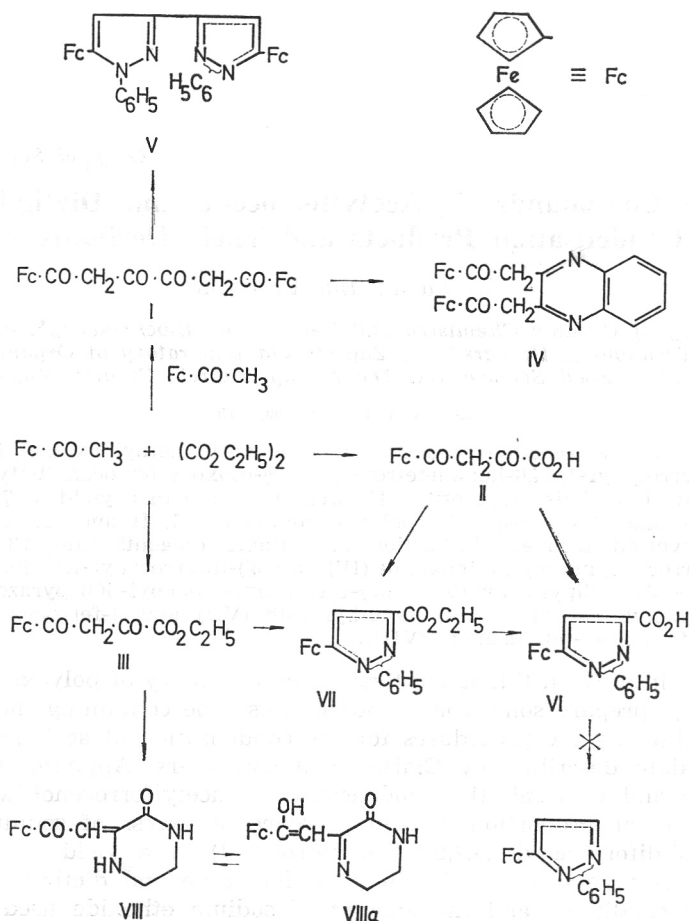
By the reaction of acetylferrocene with diethyl oxalate 1,6-diferrocenyl-1,3,4,6-hexanetetrone (I),  $\alpha,\gamma$ -dioxo- $\gamma$ -ferrocenylbutyric acid (II) and its ethyl ester (III) were prepared in a yield of 78.3, 55.1 and 51.5% resp. The polyoxo compounds I, II and III were converted through the action of suitable reagents into 2,3-bis(ferrocenoylmethyl)quinoxaline (IV), 5,5'(3')-diferrocenyl-1,1'-diphenyl-3,3'(5')-dipyrazolyl (V), 3(5)-ferrocenyl-1-phenyl-5(3)-pyrazolecarboxylic acid (VI) and its ethyl ester (VII) and 3-ferrocenoylmethylene-2-piperazinone (VIII).

Current interest in this laboratory in the chemistry of polyoxo compounds has led us to prepare some compounds of this type containing the ferrocenic residues, following the procedures for the condensation of acetophenone with diethyl oxalate described by Claisen and coworkers. Applying the method of Brömme and Claisen<sup>1</sup>, the condensation of acetylferrocene<sup>2</sup> with diethyl oxalate in molar proportion 2:1 in presence of excess of sodium ethoxide afforded 1,6-diferrocenyl-1,3,4,6-hexanetetrone (I) in a yield of 78.3%. The reaction of equimolar quantities of acetylferrocene and diethyl oxalate, depending on conditions and the amount of sodium ethoxide used<sup>3</sup> gave  $\alpha,\gamma$ -dioxo- $\gamma$ -ferrocenylbutyric acid (II) and its ethyl ester (III) in a yield of 55.1 and 51.5% resp. The products I, II and III are violet crystalline substances.

By the action of suitable reagents we converted I, II and III into heterocyclic systems containing the ferrocenic residues. The reaction of *o*-phenylenediamine and 1,6-diferrocenyl-1,3,4,6-hexanetetrone (I) yielded 2,3-bis(ferrocenoylmethyl)quinoxaline (IV), while with phenylhydrazine I gave 5,5'(3')-diferrocenyl-1,1'-diphenyl-3,3'(5')-dipyrazolyl (V)\*<sup>4</sup>.

Cyclization of  $\alpha,\gamma$ -dioxo- $\gamma$ -ferrocenylbutyric acid (II) and its ester (III) resp. with phenylhydrazine hydrochloride afforded 3(5)-ferrocenyl-1-phenyl-5(3)-pyrazolecarboxylic acid (VI) and its ester (VII). Prolonged heating of an ethanol solution of phenylhydrazine hydrochloride with  $\alpha,\gamma$ -dioxo- $\gamma$ -ferrocenylbutyric acid (II) under reflux, resulted in the esterification of the carboxyl group simultaneously with cyclization and ethyl 3(5)-ferrocenyl-1-phenyl-5(3)-pyrazolecarboxylate (VII) was isolated. By simple mixing of boiling solutions of the same components in ethanol, only 3(5)-ferrocenyl-1-phenyl-5(3)-

\* The most probable structure of the compound is presented by the formula V. However, alternative structures resulting from different enolic forms of compound I cannot be excluded. This problem was not further investigated.



-pyrazolecarboxylic acid (VI) originated. The heating of the acid (VI) did not yield 3(5)-ferrocenyl-1-phenylpyrazole by decarboxylation but ferrocene was isolated as the main product. Obviously an extensive decomposition has taken place. From ethylenediamine and ethyl  $\alpha,\gamma$ -dioxo- $\gamma$ -ferrocenylbutyrate (III) 3-ferrocenylmethylene-2-piperazinone (VIII) was prepared<sup>5</sup>.

Spectroscopic evidence supports the structure of VIII. The IR spectrum shows the following bands, characteristic for oxo derivatives of piperazine<sup>6</sup>: 3160, 1670, 1446, 1335, 998 and 810  $\text{cm}^{-1}$ . The UV spectrum\* [ $\lambda_{\text{max}}$  250  $\text{m}\mu$  ( $\epsilon$  9800),  $\lambda_{\text{max}}$  366  $\text{m}\mu$  ( $\epsilon$  18000)] corresponds to the spectrum of 3-benzoylmethylene-2-piperazinone [ $\lambda_{\text{max}}$  258  $\text{m}\mu$  ( $\epsilon$  6400),  $\lambda_{\text{max}}$  370  $\text{m}\mu$  ( $\epsilon$  17000)]<sup>5</sup>. NMR data\*\* indicate the protons of both ferrocenic and piperazinic rings with side chain. The chemical shifts of nine protons belonging to cyclopentadienyl rings of the compound VIII are identical with those of acetylferrocene<sup>7</sup>:

\* The UV spectrum (in ethanol) was recorded with a Perkin-Elmer UV/VIS Model 137 spectrometer.

\*\* The NMR spectrum of saturated deuteriochloroform solution was taken on a Varian A-60 NMR spectrometer, with tetramethylsilane as internal standard.

Ring positions*	2- 5- 3-	4- 1'- 2'- 3'- 4'- 5'-
$\delta$ (p. p. m.):	4.85 4.47	4.20

The side chain and the piperazinic ring protons appear at standard positions ( $\delta$ ): 10.24 (broad) (enol OH)\*\*, 6.34 (CH), 3.53 (broad) (ring CH<sub>2</sub>) p. p. m. Because of low resolution it was not possible to determine the coupling constants of these four piperazinic protons.

\* The unprimed numerals are used to indicate the ring positions of carbon atoms in the substituted, and primed in unsubstituted ring.

\*\* This band indicates the presence of the tautomeric form VIII a.

#### EXPERIMENTAL

The melting points were uncorrected. All IR spectra\* were recorded as KBr pellets with Perkin-Elmer Infracord Model 137 spectrometer.

#### 1,6-Diferrocenyl-1,3,4,6-hexanetetron (I)

To 50 ml. of abs. ether placed in a round bottom flask equipped with a reflux condenser 6.4 g. (0.278 mole) of sodium and 13.2 ml. (0.226 mole) of abs. ethanol was added and the resulting mixture left to stand at room temperature for twelve hours under exclusion of moisture. Then, 20.5 g. (0.090 mole) of acetylferrocene\*\* dissolved in 80 ml. of abs. ether was added followed by 6.2 ml. (0.046 mole) of diethyl oxalate, which was added dropwise through the condenser during several minutes with shaking.

For additional two hours the reaction mixture was occasionally shaken. The initial dark-red colour of the reaction mixture changed thereby to a lighter hue, and after one hour a reddish-brown solid separated. The reaction mixture was left to stand at room temperature for 24 hrs. after which time ether was allowed to evaporate spontaneously. Then the unreacted sodium was destroyed by addition of 75 ml. of ethanol. The solid was filtered off, washed with three 20 ml. portions of ethanol and after addition of ice-chips decomposed by trituration successively with ice-cold 20% hydrochloric acid. The acidified mixture was allowed to stand overnight at room temperature. The solid was separated by filtration, washed with water until neutral and suspended by stirring in 150 ml. of acetone to remove some by-products. After a repeated filtration crude I was collected (18.0 g.; 78.3%). Deep violet crystals (from cyclohexanone) m. p. 216—217.5°. IR spectrum: 1580 s (enol CO), 923 w (enol OH) cm<sup>-1</sup>.

Anal. C<sub>26</sub>H<sub>24</sub>Fe<sub>2</sub>O<sub>4</sub> (510.14) calc'd.: C 61.21; H 4.35%  
found: C 61.49; H 4.41%

#### $\alpha,\gamma$ -Dioxo- $\gamma$ -ferrocenylbutyric acid (II)

Into a boiling solution of sodium ethoxide in ethanol [from 3.7 g. (0.160 mole) sodium and 78 ml. of abs. ethanol] in a round bottom flask equipped with a reflux condenser a solution of 18.3 g. (0.080 mole) acetylferrocene and 10.8 ml. (0.080 mole) diethyl oxalate in 42 ml. of abs. ethanol was added carefully during half an hour. The reaction mixture was refluxed during subsequent 1 hour and allowed to stand at room temperature over night and then evaporated to dryness *in vacuo*. The residue was pulverized and suspended in 3 litres of ice-cold water, and filtrated from the insoluble material. The by-products were precipitated by acidification with diluted acetic acid, under vigorous mixing and cooling with ice, and separated by filtration. Addition of 20% hydrochloric acid to the filtrate precipitated 13.2 g., 55.1% raw acid II. By crystallization from 75% aqueous ethanol or from toluene,

\* The compounds I—VIII exhibit bands at about 1110 and 1000 cm<sup>-1</sup> characteristic for ferrocene derivatives having an unsubstituted ring<sup>8</sup>.

\*\* The uncrystallized material dried over phosphorus pentoxide<sup>2</sup> was used in this preparation.

a violet crystalline substance m. p. 153—154° was obtained. IR spectrum: 3100—2500 w (dimeric carboxyl OH), 1740 s (carboxyl CO), 1620 s (enol CO), 930 w (carboxyl and enol OH)  $\text{cm}^{-1}$ .

Anal.  $\text{C}_{14}\text{H}_{12}\text{FeO}_4$  (300.09) calc'd.: C 56.05; H 4.03%  
found: C 56.38; H 3.97%

*Ethyl  $\alpha,\gamma$ -Dioxo- $\gamma$ -ferrocenylbutyrate (III)*

Into an ethanol solution of sodium ethoxide [from 1.5 g. (0.065 mole) of sodium and 30 ml. of abs. ethanol] in a round bottom flask externally cooled with ice, a solution of 14.8 g. (0.065 mole) of acetylferrocene and 8.6 ml. (0.065 mole) of diethyl oxalate in 30 ml. of abs. ethanol was dropped through a reflux condenser under vigorous shaking during  $\frac{1}{2}$  hour. The reaction mixture was allowed to stand for two days at room temperature under occasional shaking and then evaporated *in vacuo* without heating. The pulverised raw material was separated from the insoluble product by suspending it in 5 litres of ice-cold water. The filtrate was acidified to pH 4 with diluted acetic acid, under cooling with ice and vigorous shaking. After standing over night 11.1 g. (51.8%) of the ester was filtered off. A sample was recrystallized from abs. ethanol as glittering deep-violet flakes m. p. 68—70.5°. IR spectrum: 1730 s (carbethoxyl CO), 1610 s (enol CO), 912 w (enol OH)  $\text{cm}^{-1}$ .

Anal.  $\text{C}_{16}\text{H}_{16}\text{FeO}_4$  (328.14) calc'd.: C 58.57; H 4.92%  
found: C 58.97; H 4.78%

The ethanol solution of the ester (III) developed a reddish-brown colour after the addition of ferrichloride and an olive-green colour after the addition of cooper acetate.

2,3-bis(*Ferrocenoylmethyl*)quinoxaline (IV) was prepared by refluxing equimolar quantities of I and *o*-phenylenediamine in abs. ethanol during two hours. By recrystallization from acetic anhydride : cyclohexanone (1:2), red crystals were obtained m. p. 220—222°.

Anal.  $\text{C}_{32}\text{H}_{26}\text{FeN}_2\text{O}_2$  (582.25) calc'd.: C 66.01; H 4.50; N 5.50%  
found: C 66.29; H 4.25; N 5.52%

*5,5'(3')-Diferrocenyl-1,1'-diphenyl-3,3'(5')-dipyrazolyl (V)*

A mixture of 2 g. (0.004 mole) of I, 0.9 g. (0.008 mole) of phenylhydrazine and 6 ml. of glacial acetic acid was heated on a water bath for three hours with occasional shaking. The separated solid was filtered off after cooling, and washed with acetic acid and water. The crude product (1.0 g.; 39%) was recrystallized for analysis from dimethylformamide as pale-yellow crystals, which did not melt under 305°, but partly carbonized. IR spectrum\*: 1600 m (pyrazolic C=N), 1570 m (pyrazolic C=C), 1450 m (unassigned pyrazolic band)  $\text{cm}^{-1}$ .

Anal.  $\text{C}_{38}\text{H}_{30}\text{Fe}_2\text{N}_4$  (654.40) calc'd.: C 69.74; H 4.62; N 8.56%  
found: C 70.02; H 4.83; N 8.48%

*3(5)-Ferrocenyl-1-phenyl-5(3)-pyrazolecarboxylic acid (VI)*

Into the boiling solution of 7.4 g. (0.025 mole) of II in 34 ml. of 96% ethanol a boiling solution of 5.4 g. (0.037 mole) of phenylhydrazine hydrochloride in 130 ml. of 96% ethanol was added. The reaction mixture was slowly cooled down to the room temperature and allowed to stand over night in a refrigerator; a cinnamon coloured product was filtered off and from the filtrate was separated additional quantity of brown product (0.5 g.) after gradual addition of 100 ml. of water (total yield 55%). By crystallization from dioxane, a yellow crystalline substance m. p. 219—221° (with carbonization) was obtained. IR spectrum: 3100—2500 w (di-

\* The pyrazolic bands of the compounds V, VI and VII have been assigned according to reference<sup>7</sup>.

meric carboxyl OH), 1710 s (carboxyl CO), 1610 w (pyrazolic C=N), 1570 m (pyrazolic C=C), 1450 m (unassigned pyrazolic band), 932 m (carboxyl OH)  $\text{cm}^{-1}$ .

*Anal.*  $\text{C}_{20}\text{H}_{16}\text{FeN}_2\text{O}_2$  (373.20) calc'd.: C 64.54; H 4.34; N 7.53%  
found: C 64.64; H 4.40; N 7.27%

### *Ethyl 3(5)-Ferrocenyl-1-phenyl-5(3)-pyrazolecarboxylate (VII)*

The ester (VII) was prepared as described above for acid (VI), starting with the ethyl  $\alpha,\gamma$ -dioxo- $\gamma$ -ferrocenylbutyrate (III) and phenylhydrazine hydrochloride. After standing for twelve hours at room temperature the separated golden-yellow needle-shaped crystals were filtered off and from the filtrate under addition of water an additional quantity of a brownish substance (total yield 91%) was precipitated. By the crystallization from abs. ethanol, a yellow crystalline substance m.p. 148.5—150° was obtained. IR spectrum: 1710 s (carbethoxyl CO), 1600 w (pyrazolic C=N), 1570 (pyrazolic C=C), 1450 (unassigned pyrazolic band).

*Anal.*  $\text{C}_{22}\text{H}_{20}\text{FeN}_2\text{O}_2$  (400.25) calc'd.: C 66.06; H 5.03; N 7.00%  
found: C 66.00; H 5.30; N 6.93%

The ester VII can be prepared in a yield of 78% by refluxing the ethanol solution of  $\alpha,\gamma$ -dioxo- $\gamma$ -ferrocenylbutyric acid (II) and phenylhydrazine hydrochloride (in molar proportion 1:2) and by treating the reaction mixture in a similar way as described above. By crystallization from abs. ethanol, a yellow crystalline substance, m.p. 149—150.5° was obtained. The mixed m.p. showed no depression (with the above described ester).

Ethyl 3(5)-ferrocenyl-1-phenyl-5(3)-pyrazolecarboxylate (VII) can be hydrolyzed into the acid VI in 83% yield by action of sodium hydroxide in aqueous ethanol solution and acidification with diluted hydrochloric acid.

### *3-Ferrocenylmethylene-2-piperazinone (VIII)*

Into a boiling solution of 0.98 g. (0.003 mole) of the ester III in 60 ml. of 96% ethanol a solution of 0.3 g. (0.004 mole) of ethylenediamine in 6 ml. of 96% ethanol was added. The reaction mixture was refluxed for 1½ hour and the solvent evaporated *in vacuo* until dry. The residue was treated with 10 ml. of 2 N hydrochloric acid, filtered and washed with water until neutral (0.72 g.; 73%). Crystallization from 96% ethanol, amorphous brick-coloured substance m.p. 217—220°. The spectral data are presented in the theoretical part of this paper.

*Anal.*  $\text{C}_{16}\text{H}_{16}\text{FeN}_2\text{O}_2$  (324.15) calc'd.: C 59.28; H 4.99; N 8.65%  
found: C 59.32; H 5.23; N 8.87%

*Acknowledgment.* The authors wish to express their thankfulness for interpretation of spectrometric data to Professor Z. Štefanac (Institute for Medical Researches, Zagreb) and Dr. Z. Meić (Institute »Ruđer Bošković«, Zagreb) and also to Professor D. Hadži (Chemical Institute »Boris Kidrič«, Ljubljana) for helpful discussions.

#### REFERENCES

1. E. Brömme and L. Claisen, *Chem. Ber.* **21** (1888) 1134.
2. P. J. Graham and R. V. Lindsey, *J. Am. Chem. Soc.* **79** (1957) 3416.
3. C. Beyer and L. Claisen, *Chem. Ber.* **20** (1887) 2178.
4. I. L. Finar, *J. Chem. Soc.* **1955** 1205.
5. V. A. Zagorevskij, D. A. Zikov, and E. K. Orlova, *Zh. Obšč. Him.* **34** (1964) 539.
6. Tatsuo Miyazawa, *J. Mol. Spectr.* **4** (1960) 156; R. L. Hodgson, I. R. C. Bick and D. J. Cram, *J. Am. Chem. Soc.* **76** (1954) 1137.
7. K. L. Rinehart, Jr., D. E. Bublitz, and D. H. Gustafson, *J. Am. Chem. Soc.* **85** (1963) 970.
8. C. R. Hauser and C. E. Cain, *J. Org. Chem.* **23** (1958) 1142; C. E. Cain, T. A. Mashburn, Jr. and C. R. Hauser, *J. Org. Chem.* **26** (1961) 1030.

## IZVOD

## Kondenzacioni produkti acetilferocena i dietiloksalata i njihovi derivati

M. Lačan i V. Rapić

Kondenzacijom acetilferocena i dietiloksalata pripremljeni su ovisno o uvjetima i molarnim omjerima 1,6-diferocetil-1,3,4,6-heksantetron (I),  $\alpha,\gamma$ -diokso- $\gamma$ -ferocetilmaslačna kiselina (II) i njen etilni ester (III). Ovi polioksospojevi prevedeni su djelovanjem pogodnih reagensa u 2,3-bis(ferocenoilmetil)kinoksalin (IV), 5,5'(3')-diferocetil-1,1'-difetil-3,3'(5')-dipirazolil (V), 3(5)-ferocetil-1-fetil-5(3)-pirazolkarbonsku kiselinu (VI) i njen etilni ester (VII) i 3-ferocenoilmetilen-2-piperazinon (VIII).

TEHNOLOŠKI FAKULTET

I

PREHRAMBENO-TEHNOLOŠKI INSTITUT  
ZAGREB

Primljeno 30. siječnja 1970.