

Ferrocene Compounds. XXXV.* Reactions of 1,1'-Ferrocenylenebis(carbinyl acetate) and Derived Quaternary Iodide with Hydroxyalkanoates

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Biscarbinol, 1,1'-Fn[CH(CH₃)OH]₂ (**1**), and the corresponding bis(carbinyl acetate) **2** were prepared according to the described procedures. Amination of bisacetate **2** with Me₂NH and subsequent quaternization of the intermediate amine **3** gave iodide **4**. By the action of alkoxides derived from methyl glycolate and methyl lactate on acetate **2** or salt **4**, unsaturated ether **5** (8–22 %), unsaturated esters **6a** (**6b**) (2–18 %) and ester-ethers **7a** (**7b**) (6–15 %) were obtained. The structure of heteroannularly substituted nonsymmetric ferrocene derivatives **5–7** was undoubtedly confirmed by elemental and spectroscopic analyses, and the reaction mechanisms of their formation were proposed.

Key words

- α,α' -(1,1'-ferrocenylene)bisethanol
- α,α' -(1,1'-ferrocenylene)bis(ethyl acetate) and derived quaternary iodide
- methyl glycolate
- methyl lactate

INTRODUCTION

To our knowledge there are not many papers dealing with ferrocenyloxaaliphatic acids, Fc(CH₂)_mO(CH₂)_nCOOH ($m, n = 0, 1, 2, 3\dots$), and their derivatives. Only a few ferrocenyloxyaliphatic acids, FcO(CH₂)_nCOOH, are known. Thus, for instance, ferrocenyloxyacetic acid is described as a condensation product of ferrocenyl alcohol with chloroacetic acid in an aqueous solution of potassium hydroxide.²

In continuation of our programme on the chemistry of ferrocene heteroaliphatic acids and the derived α - and β -ferrocenylcarbenium ions^{3–5}, we have described the synthesis and reactions of new types of ferrocenyloxaaliphatic acid esters, FcCHR(OCHR')COOMe (R = H, Me, Ph; R' = H, Me).⁴ These compounds have been prepared by the reaction of alkoxides derived from methyl

glycolate or methyl lactate with the corresponding *N,N,N*-trimethylferrocylammonium iodides¹ (ferrocyl = ferrocenyl-methyl) or ferrocenylcarbinyl acetates. The resultant esters were accompanied by a small quantity of oligomeric esters, FcCHR(OCHR')CO_nOMe, and by some ferrocyl methyl ethers. As opposed to the alkaline hydrolysis of the analogous methyl benzoxyacetate into benzoxyacetic acid, acidification of sodium alkanooates obtained by saponification of the mentioned ferrocene esters unexpectedly gave the corresponding ferrocenylcarbinols. In a similar way, these esters were converted into mixtures of the mentioned carbinols and diferrocyl ethers by the action of aqueous hydrochloric acid.

In this paper we are reporting about reactions of heteroannularly substituted ferrocene bisacetate and bisquaternary salt with methyl glycolate and methyl lactate.

* For Part XXXIV, see Ref. 1.

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RESULTS AND DISCUSSION

α,α' -(1,1'-Ferrocenylene)bis(ethyl acetate) (82 %) (**2**) was obtained by modification of the described procedure:⁶ instead of refluxing the pyridine solution of biscarbinol **1** and acetic anhydride, the reaction was performed at 0 °C and thereupon under stirring for a longer time at room temperature. An attempt to prepare bisquaternary salt **4** by hydrogenation of 1,1'-diacetylferrocene bisoxime and quaternization of the bisamine formed failed. The desired salt **4** in 62 % yield was successfully synthesized by reaction of bisacetate **2** with Me₂NH in methanol, and quaternization of the obtained 1,1'-bis[α -(dimethylamino)ethyl]ferrocene (**3**) (70 %) by MeI in acetone at 0 °C.

N,N,N-Trimethylferrocylammonium iodides or ferrocyl acetates were refluxed for 1–3 hours with methyl hydroxyalkanoates in the presence of sodium (mole ratio 1 : 5 : 3.5) giving the desired ferrocylalkanoates, FcCHROCHR'COOMe (R = H, Me, Ph; R' = H, Me).⁴

Our experiments with bisacetates **2** or bisquaternary salts **4** were achieved in a similar way, aimed at linking oxaliphatic chains to both cyclopentadiene rings of ferrocene reagents. However, instead of the planned symmetrically substituted products, 1,1'-ferrocenylenebis(oxaliphatic esters) **8**, refluxing of 0.70–1.12 mmol of reagents **2** or **4** with 1.47–6.7 mmol of sodium alkoxides derived from methyl glycolate or methyl lactate in excess of these

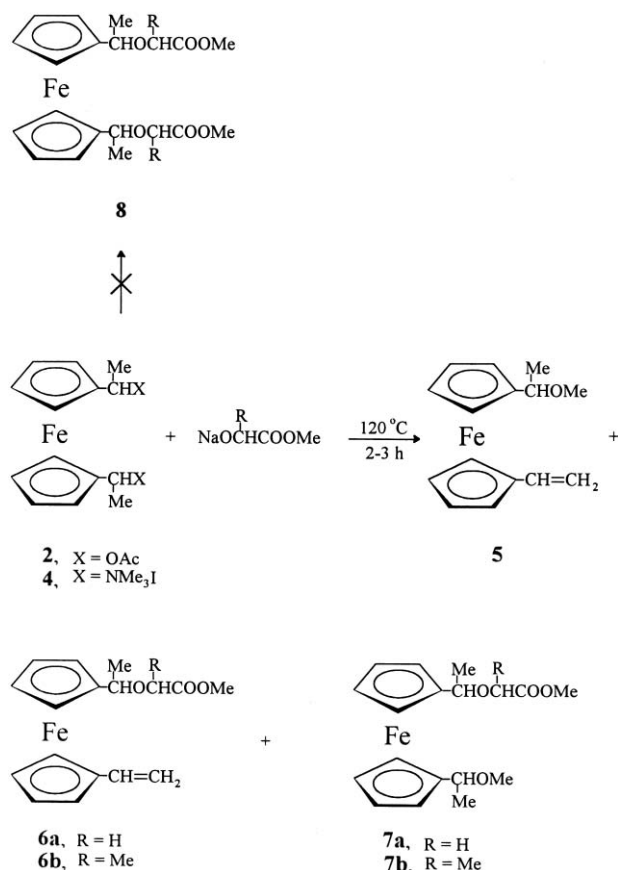


TABLE I. Yields for:

esters for 2–3 h gave mixtures of 8–22 % of unsaturated ether **5**, 2–18 % of unsaturated esters **6**, and 6–12 % of ether-esters **7** (Scheme 1, Table I).

Formation of accompanying ferrocyl methyl ethers, FcCHROCH₃, in our previous paper⁴ was explained by *O*-ferrocenylalkylation of methoxy oxygen of the starting aliphatic hydroxyesters by the corresponding ferrocene reagents; this intermediate oxonium species were subsequently cleaved (AC1 mechanism) supposing the ethers were thermodynamically more stable than esters.

The mechanisms of reactions **2 / 4** → **5** could be rationalized in a similar way. Having in mind the fact that in the course of FcCHROCHR'COOMe and FcCHROCH₃ preparation⁴ formation of the corresponding unsaturated product was not observed, one can assume that oxonium **A** was a product of kinetic control generated in the first reaction step (probably by S_N1 mechanism). This intermediate was thereupon cleaved giving intermediate **B** (AC1), which underwent elimination into unsaturated ether **5** by the action of alkoxide (iii).

Formation of unsaturated esters **6** can be explained by S_N transformations of ferrocene substrates **2 / 4** with alkoxides (iii). Primarily generated intermediate **C**, presumably the product of kinetic control, was thereafter transformed by elimination reaction into unsaturated esters **6** in a similar way as described above. On the other side, **C** can be ferrocenylalkylated into oxonium **D**, which gave ether-esters **7** by AC1-reaction (Scheme 2).

It should be emphasized that all the described substitution and elimination reactions are most probably monomolecular, because the corresponding intermediate α -ferrocenylcarbenium ions are extraordinarily stable.⁷

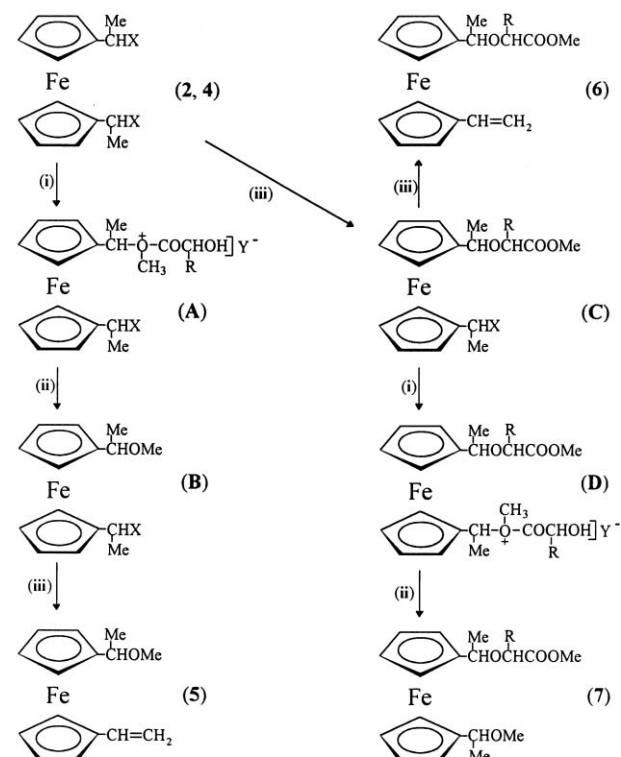
The structure of the compounds prepared was unambiguously confirmed by spectrometric analysis. Ester function of compounds **6** and **7** was registered as strong signals at 1754–1759 and 1738–1742 cm⁻¹. Absorption of medium intensity in the spectra of compounds **5** and **6** at \approx 1630 cm⁻¹ corresponded to the vinyl group. ¹H NMR

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Scheme 1.



(i) HOCH(R)COOMe, X = OAc, NMe₃I; (ii) -HOCH(R)COY, X = OAc, NMe₃I, Y = OAc, I; (iii) NaOCH(R)COOMe, X = OAc, NMe₃I.

Scheme 2.

spectra of all the unsaturated compounds contained a similar pattern for this group: H_α at ≈ 6.42 dd, H_β at ≈ 5.33 d and H_γ at 5.05 d ppm. Methyl protons of methoxycarbonyl and methoxy groups gave singlets at 3.72–3.76 and 3.25–3.27 ppm. It is noteworthy that ¹H NMR spectra of compounds **6b**, **7a** and **7b**, possessing 2 or 3 chiral centers, contained signals that indicated the presence of the expected diastereomerically related enantiomeric pairs. *E.g.*, in the spectrum of **7a** (2 chiral centers) two discrete signals at 4.01 and 4.02 ppm, corresponding to methylene groups of these forms, were found. ¹³C NMR spectra of compounds **6** and **7** contained signals at 51.36–51.59 ppm for methyl C-atoms and 171.02–174.28 ppm corresponding to carbonyl C-atoms of methoxycarbonyl group. Methyl C-atoms of the methoxy group in the compounds **5** and **7** gave signals at 55.35–55.51 ppm. Methyne and methylene C-atoms from the vinyl group in compounds **5** and **6** gave the expected signals at 133.91–134.15 and 111.28–111.46 ppm.

EXPERIMENTAL

Melting points were determined with a Buechi apparatus. The IR spectra were recorded for CCl₄ solutions with a Bomem MB100 Mid FT IR spectrophotometer. The ¹H and ¹³C NMR spectra of CDCl₃ solutions were recorded on a

Varian EM 360 or Varian Gemini 300 spectrometer with tetramethylsilane as internal standard. Products were purified by preparative thin layer chromatography on silica gel (Merck, Kieselgel 60 HF₂₅₄) using dichloromethane and mixtures dichloromethane-ethanol as eluents and/or by recrystallization from (aqueous) ethanol.

Reduction of the 1,1'-diacetylferrocene gave α,α'-(1,1'-ferrocenylene)bisethanol (**1**).⁸

α,α'-(1,1'-Ferrocenylene)bis(ethyl acetate) (**2**)

Acetic anhydride (1.3 g, 12.69 mmol) was added at 0 °C to a solution of biscarbinol **1** (300 mg, 1.09 mmol) in pyridine (2 ml). After mechanical stirring at room temperature overnight, the reaction solution was evaporated to dryness to give bisacetate **2** (Ref. 6) (324.6 mg, 82 %), which was used directly in the next reaction step without any purification.

1,1'-Bis[α-(dimethylamino)ethyl]ferrocene (**3**) and the Corresponding Bis(methyl iodide) (**4**)

Aqueous solution (70 %) of dimethylamine (1.6 g, 35.48 mmol) was added to a solution of crude acetate **2** (1.0 g, 2.8 mmol) in methanol (23 ml). The mixture was stirred at room temperature for 48 hours. Thereby the yellow-brownish colour turned to red-brownish. Methanol was evaporated, diethyl ether was added and the solution was acidified to pH ≈ 1 with aqueous phosphoric acid (15 ml, w = 0.085). After separating from organic layer, the acidic aqueous phase, containing the resulting ammonium salt, was extracted once more with diethyl ether to remove unreacted biscarbinol **1**. Aqueous phase was basified with solid Na₂CO₃ to pH ≈ 10, the resulting amine was extracted with diethyl ether, washed with saturated aqueous solution of sodium chloride, dried over Na₂SO₄, and evaporated to dryness to yield the red-brownish oily bisamine **3** (Ref. 9) (645 mg, 70 %).

IR (CCl₄) ν_{max}/cm⁻¹: 3093 m (C–H) arom., 2937 s, 2858 m, 2820 s, 2780 s (C–H) aliph.; ¹H NMR (CDCl₃) δ/ppm: 4.07 (m, 8H, Fn), 3.61 (q, 2H, FnCH), 1.45 (d, 6H, CCH₃), 2.08 (m, 12H, NMe₂).

Solution of MeI (20.41 g, 143.8 mmol) in acetone (15 ml) was added dropwise to a solution of crude bisamine **3** (1.02 g, 3.11 mmol) in acetone (30 ml) at 0 °C under mechanical stirring. By addition of diethyl ether, dark yellow to brownish crystals of quaternary salt **4** precipitated (951.5 mg, 62 %). m. p. 163–164 °C.

General Procedure for Preparation of Compounds 5–7

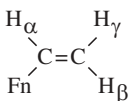
Sodium (115 g, 5 mmol) was added under vigorous mechanical stirring to methyl glycolate or methyl lactate (80 mmol). After formation of the corresponding sodium alkoxides, acetate **2** or quaternary salt **4** (0.8 mmol) was added and the reaction solution was refluxed for 1–4 hours. The mixture was cooled to room temperature, poured into a double volume of water and extracted with dichloromethane. The organic layer was washed with saturated

TABLE II. Physical constants and IR spectral data for:

Compd. no.	R	Formula (M_r)	Anal. calcd. (found) / %		$\tilde{\nu}_{\max} / \text{cm}^{-1}$			
			C	H	ν (CH) Fc	ν (CH) alif.	ν (C=O)	ν (C=C)
5	–	C ₁₅ H ₁₈ FeO (270.1)	66.72 (66.88)	6.72 (6.41)	3090 m	2980 s 2935 m 2817 w	–	1630 m
6a	H	C ₁₇ H ₂₀ FeO ₃ (328.2)	62.21 (62.02)	6.14 (6.31)	3090 m	2981 m 2935 m	1759 s 1741 s	1630 m
6b	CH ₃	C ₁₈ H ₂₂ FeO ₃ (342.2)	63.18 (63.35)	6.48 (6.22)	3091 w	2979 s 2936 m 2870 w	1755 s 1737 s	1631 m
7a	H	C ₁₈ H ₂₄ FeO ₄ (360.2)	60.02 (60.29)	6.72 (6.58)	3095 w	2978 s 2937 m	1759 s 1742	–
7b	CH ₃	C ₁₉ H ₂₆ FeO ₄ (374.2)	60.98 (60.72)	7.00 (7.23)	3096 w	2978 s 2937 m 2897 m	1754 s 1738 s	–

TABLE III. ¹H NMR spectral data (δ /ppm) for:

Compd. no.	R	Ferrocene protons	Aliphatic protons ^(a)										COOMe	CHOMe	
			a		b		c		CH=CH ₂						
			CH(α)	CH ₃ (β)	CH(α)	CH ₃ (β)	CH(α)	CH ₂	CH ₃ (β)	(α)	(β)	(γ)			
5	–	4.19 (8, bm)	3.81 (1, q)	1.52 (3, d)	–	–	–	–	–	–	6.42 (1, dd)	5.32 (1, d)	5.05 (1, d)	–	3.25 (3, s)
6a	H	4.18 (8, bm)	–	–	4.47 (1, q)	1.60 (3, d)	–	4.01 (2, s)	–	–	6.41 (1, dd)	5.33 (1, d)	5.05 (1, d)	3.72 (3, s)	–
6b ^(c)	CH ₃	4.19 (10, bm)	–	–	^(b)	1.62 (3, m)	^(b)	–	1.35 ^(d) (3, d)	–	6.43 (1, dd)	5.33 (1, d)	5.05 (1, d)	3.76 ^(e) (3, s)	–
7a ^(c)	H	4.14 (9, bm)	^(b)	1.53 (3, m)	4.43 (1, m)	1.62 (3, m)	–	4.01 s 4.02 s (2)	–	–	–	–	–	3.72 (3, bs)	3.25 (3, bs)
7b ^(c)	CH ₃	4.11 (11, bm)	^(b)	1.53 (3, m)	4.40 (^(b) , m)	1.60 (3, m)	^(b)	–	1.35 ^(f) (3, d)	–	–	–	–	3.75 ^(g) (3, s)	3.27 (3, s)

^(a) The following coupling constants were measured: for CH–CH₃ $^3J_{\alpha,\beta} \approx 6$ Hz, for  $^3J_{\alpha,\beta} \approx 17$, $^3J_{\alpha,\gamma} \approx 11$ and $^2J_{\beta,\gamma} \approx 0$ Hz.

^(b) Broad multiplets typical of ferrocene protons include designated signals too.

^(c) Observed multiplets, broad singlets and two singlets for CH₂ (*c*) of compound **7a** indicate the presence of the corresponding stereoisomers. Additional singlets are present as follows: ^(d) 1.31 d, 1.29 d; ^(e) 3.65 s; ^(f) 1.30 d; ^(g) 3.64 s (indicating the presence of oligomers).

TABLE IV. ^{13}C NMR spectral data (δ/ppm) for:

Compd. no.	R	Ferrocene C-atoms		Methyne C-atoms			Methylene C-atoms			Methyl C-atoms		COO			
		CH	C	<i>a</i>	<i>b</i>	<i>c</i>	CH=CH ₂	<i>c</i>	CH=CH ₂	<i>a</i>	<i>b</i>	<i>c</i>	OCH ₃	COOCH ₃	
		$\text{Fn}(\overset{\text{CH}_3}{\text{C}}\text{H}_a\text{OMe})\text{CH}=\text{CH}_2$ (5), $\text{Fn}(\overset{\text{CH}_3}{\text{C}}\text{H}_b\text{OCH}_c\text{COOMe})\text{CH}=\text{CH}_2$ (6a , 6b), $\text{Fn}(\overset{\text{CH}_3}{\text{C}}\text{H}_b\text{OCH}_c\text{COOMe})\text{CH}_a\text{OMe}$ (7a , 7b)													
5	–	66.98–70.02 (8)	83.71 89.91	74.50	–	–	134.02	–	111.28	21.95	–	–	55.45	–	–
6a	H	66.92–69.98 (8)	83.83 88.06	–	73.76	–	133.91	64.70	111.44	–	19.87	–	–	51.57	171.09
6b	CH ₃	66.55–69.64 (8)	83.69 88.06	–	74.39	71.82	134.15	–	111.46	–	19.58	18.92	–	51.46	171.85
7a	H	66.56–70.02 (8)	88.92 90.42	74.59	73.93	–	–	64.76	–	24.97	19.87	–	55.51	51.59	171.02
7b	CH ₃	65.98–69.07 (8)	89.34 90.50	74.51	72.71	71.92	–	–	–	21.06	19.65	18.74	55.35	51.36	174.28

aqueous solution of sodium chloride, dried over Na_2SO_4 , and evaporated to dryness to give yellow-brownish resinous products, which were separated into compounds **5–7** by preparative thin layer chromatography using the mixture dichloromethane-ethanol (30:1) as eluent (Tables I–IV).

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SAŽETAK

Ferrocenski spojevi. XXXV. Reakcije 1,1'-ferocenilenbis(karbinil-acetata) i izvedenoga kvaternog jodida s hidroksialkanoatima

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Prema postupcima opisanim u literaturi pripremljen je biskarbinol 1,1'-Fn[CH(CH₃)OH]₂ (**1**) koji je preveden u odgovarajući bis(karbinil-acetat) **2**. Aminiranjem bisacetata **2** s Me₂NH i kvaternizacijom intermedijarnoga amina **3** dobiven je jodid **4**. Djelovanjem alkoksida izvedenih iz metil-glikolata ili metil-laktata na acetat **2** odnosno sol **4** pripravljeno je 8–22 % nezasićena etera **5**, 2–18 % nezasićenih estera **6a** (**6b**) i 6–15 % eter-estera **7a** (**7b**). Struktura heteroanularno supstituiranih nesimetričnih ferocenskih derivata **5–7** nedvoumno je potvrđena na temelju elementarne i spektroskopske analize te su predloženi reakcijski mehanizmi njihova nastajanja.