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Ferrocene Compounds. VIII*. The Stobbe Condensations of Acylferrocenes with Diethyl Succinate

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The Stobbe condensations of formyl-, acetyl-, and benzoylferrocene, resp., with diethyl succinate gave mixtures of (*E*)- and (*Z*)-stereoisomeric products, $\text{FcCR}=\text{C}(\text{CO}_2\text{Et})\text{CH}_2\text{CO}_2\text{H}$ ($\text{R}=\text{H}$, Me, and Ph, resp.). These mixtures have been separated into pure compounds by chromatographic methods, and their structures have been assigned by spectroscopic means.

INTRODUCTION

The Stobbe condensations of aromatic aldehydes with succinic esters give predominantly the (*E*)-arylidenesuccinic half esters¹. Reactions of unsymmetrical aryl ketones with succinic esters do not show such a stereoselectivity; for example, in the condensation of acetophenone with diethyl succinate a 1:1 mixture of (*E*)- and (*Z*)-2-benzylidenesuccinic half esters is obtained². Surprisingly, Touchard and Dabard³ reported the formation of pure (*Z*)-stereoisomer in the condensation of acetylferrocene with dimethyl succinate.

In connection with our previous paper⁴ it seemed interesting to investigate the condensation of formylferrocene with diethyl succinate. In this work we are reporting also reinvestigations of results described in reference 3.

RESULTS AND DISCUSSION

The reactions of acylferrocenes with diethyl succinate are achieved under the conditions described in our previous paper⁴. In the condensation of formylferrocene two acidic reaction products were isolated, showing the same neutralization equivalent corresponding to the molecular weight of I. The separation of the products can be performed much more successfully after their conversion into the corresponding mixture of mixed esters II by means of preparative thin-layer chromatography.

In the ¹H NMR spectrum of the first fraction of reaction product II (with higher R_F -value) the olefinic proton gave a signal at δ 7.53, and in the second fraction at δ 7.63. It may be assumed⁵ that an olefinic proton (or methyl group protons — see below) *cis* to the ethoxycarbonyl group gives a signal at a lower

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- I, $\text{R}=\text{R}^1=\text{H}$, $\text{R}^2=\text{Et}$
 II, $\text{R}=\text{H}$, $\text{R}^1=\text{Me}$, $\text{R}^2=\text{Et}$
 III, $\text{R}=\text{R}^1=\text{R}^2=\text{H}$
 VI, $\text{R}=\text{Me}$, $\text{R}^1=\text{H}$, $\text{R}^2=\text{Et}$
 (E)- VII, $\text{R}=\text{R}^1=\text{Me}$, $\text{R}^2=\text{Et}$ (Z)-
 VIII, $\text{R}=\text{R}^1=\text{R}^2=\text{Me}$
 IX, $\text{R}=\text{Ph}$, $\text{R}^1=\text{H}$, $\text{R}^2=\text{Et}$
 X, $\text{R}=\text{Ph}$, $\text{R}^1=\text{Me}$, $\text{R}^2=\text{Et}$
 XI, $\text{R}=\text{Ph}$, $\text{R}^1=\text{H}$, $\text{R}^2=\text{Me}$
 XII, $\text{R}=\text{Ph}$, $\text{R}^1=\text{R}^2=\text{Me}$

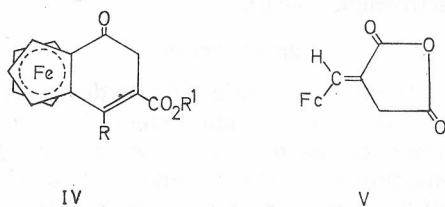


Figure 1.

field than in the *trans* arrangement, owing to the deshielding effect of the carbonyl group. On the other hand the UV spectrum of the second fraction [$\lambda_{\text{max}} = 248$ ($\epsilon = 12\,600$); $\lambda_{\text{max}} 294$ nm ($\epsilon = 14\,300$)] shows greater extinction coefficients than the spectrum of the first fraction [$\lambda_{\text{max}} 246$ ($\epsilon = 11\,400$); $\lambda_{\text{max}} 294$ nm ($\epsilon = 12\,100$)]. Consequently, to the second fraction the (*E*)-configuration should be assigned while the first one would correspond to (*Z*)-II configuration. From the ratio of the corresponding methoxycarbonyl signals in the ^1H NMR spectrum of the total product II the ratio of (*E*)- and (*Z*)-II (82 : 18) was determined using the method described in references 3 and 6. A similar result was obtained by weighing the chromatographic fractions of samples I and II resp.

In order to confirm the above stereochemical assignments we tried to cyclise samples of (*E*)- and (*Z*)-I, resp., to the compound IV ($\text{R} = \text{H}$, $\text{R}^1 = \text{Et}$) by means of polyphosphoric acid or trifluoroacetic anhydride^{3,7}. Surprisingly these attempts failed despite to rather severe reaction conditions.

The alkaline hydrolysis of the compound (*E*)-I gave the corresponding diacid (*E*)-III (UV spectra!) which upon a trifluoroacetic anhydride treatment

afforded anhydride V. It should be noted that the yields of this anhydride were considerably lower than of α -ferrocenylmethyleneglutaric anhydride⁴. This fact could be rationalized in terms of a greater strain in this class of five membered ring anhydrides than in the corresponding six membered ring compounds (IR spectra!). Attempts to convert anhydride V to IV ($R = R^1 = H$) by intramolecular Friedel-Crafts acylation failed.

The rather surprising results of the Stobbe condensation of acetylferrocene with dimethyl succinate³ (see Introduction) prompted us to reexamine this reaction. Instead of dimethyl succinate³ we used, as in our previous experiments⁴, diethyl succinate, which is more convenient for the NMR determination⁶ of ratios of isomers formed in this reaction. The condensation of acetylferrocene with diethyl succinate gave in our hands a mixture of two isomeric half esters VI. The separation of these isomers and the assignment of their configuration was carried out as described above: in the ¹H NMR spectrum of the first chromatographic fraction (higher UV extinction coefficients) of compound VII, the methyl group on the double bond gave a signal at δ 2.52, and in the second fraction (lower UV extinction coefficients) the signal was at δ 2.24. It may be concluded that the first fraction consists of (*E*)- and the second of (*Z*)-VII. The NMR spectrum of the isomer (*E*)-VII very closely resembles that of the previously described compound VIII (the distinctions clearly appeared in the region of ethoxycarbonyl and corresponding methoxycarbonyl signals) and similarly the corresponding IR spectra. The conclusion must be made that the (*Z*)- stereochemical assignment of the described compound VIII was wrong, and that it should be (*E*)- as in (*E*)-VII. The ratio of (*E*)- and (*Z*)-VII is found to be 75 : 25 using the above described methods.

Also, the assignment of structure to the (*E*)- and (*Z*)-isomers of XI³ is not convincing in our opinion. In the ¹H NMR spectra of the corresponding diesters XII³, the only significant chemical-shift difference is that between the CH_2CO_2Me signals ($\Delta\delta \approx 1$). It could be argued that the isomer giving the higher-field CH_2 resonance (δ 3.08), which has been assigned to the (*E*)-stereochemistry by the authors, is in fact the (*Z*)-isomer in which the CH_2 group would be located in the shielding region of the *cis*-phenyl group.

In our base-induced condensation experiments of benzoylferrocene with diethyl succinate a 42 : 58 (first : second chromatographic fraction) mixture of stereoisomers of half ester IX was obtained. The differences in the ultraviolet absorption spectra cannot be interpreted with certainty since both isomers incorporate $FcC=CCO_2Et$ as well as $PhC=CCO_2Et$ chromophores. The ¹H NMR spectra of the stereoisomers of the corresponding diester X, very closely resemble that of XII; consequently, to the first chromatographic fraction one could assign the (*E*)-, and to the second fraction the (*Z*)-configuration.

Contrary to the (*E*)-2-ferrocenylmethyleneglutaric half ester⁴ the (*E*)-I, (*E*)-VI, and (*E*)-IX are found to isomerise in the presence of base. This distinction could be interpreted according to the mechanism for the isomerisation of benzylidenesuccinic esters proposed by Heller⁵. This mechanism obviously cannot be applied to the isomerisation of the Stobbe condensation

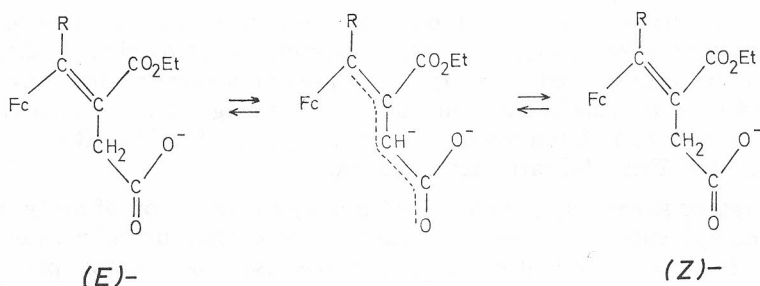


Figure 2.

products with glutaric esters^{4,8}. The lack of stereoselectivity in the Stobbe condensations involving acylferrocenes and diethyl succinate, contrary to the condensation of formylferrocene with diethyl glutarate⁴, can be partly interpreted in terms of these isomerizations.

EXPERIMENTAL

The same techniques and apparatus were used as described previously⁴. In addition, high-pressure-liquid-liquid-chromatography⁹ was carried out with an apparatus consisting of an Altex Mod 110 pump, a μ -PORASIL (Waters) 1/4" \times 30 cm column and a Schoefel SF 770 UV-detector (275 nm); eluent *n*-hexane : dioxane (3 : 1); flow rate 0.5 ml min⁻¹.

Condensation of Acylferrocenes with Diethyl Succinate (I, VI, and IX)

General procedure. — 1.1 g (37 mmol) of potassium was dissolved in 50 ml of absolute *tert*-butanol and a solution of 6.6 g (36 mmol) of diethyl succinate and 25 mmol of the appropriate acylferrocene in the same solvent were added successively over a period of 1/4 hour with good stirring at reflux temperature. After refluxing for 1/2 hour the solvent was evaporated and the residue worked up in the usual manner. The resulting crude mixtures of (*E*)- and (*Z*)- I, VI, and IX, resp., were separated on preparative TLC plates in benzene : ethanol (v/v) 15 : 1 or 30 : 1 (see Tables I and II).

Esterification of Half Esters I, VI, and IX, resp., (II, VII, and X, resp.)

General procedure. — Esterification of the separated (*E*)- and (*Z*)-I, VI and IX, resp., as well as of the corresponding crude (*E*, *Z*)-mixtures was performed by the action of ethereal diazomethane. In the latter case the resulting (*E*, *Z*)-methyl ethyl esters II, VII, and X, resp., were separated into components by means of preparative TL chromatography using benzene or benzene : ethanol 30 : 1 as eluents (see Tables I and II).

(*E*)-2-Ferrocenylmethylenesuccinic Acid (III)

1.5 g (4.4 mmol) of half ester (*E*)-I was refluxed in a solution of methanolic potassium hydroxide containing some water for 1 hour. The reaction mixture was evaporated to dryness and worked up as usual giving 1.3 g (95%) of III; a sample for analysis was crystallized from ethanol : water 1 : 2; m. p. 173–5 °C. IR spectrum (KBr): 1680 (s) ($\nu_{C=O}$ conjugated), 170 (sh) ($\nu_{C=O}$ unconjugated) and 1633 cm⁻¹ (s) ($\nu_{C=C}$); UV spectrum: λ_{max} 242 ($\epsilon = 12\,100$) and λ_{max} 290 nm ($\epsilon = 13\,100$).

Anal. C₁₅H₁₄FeO₄ (314.1) calc'd.: C 57.36; H 4.49%
found: C 57.65; H 4.78%

Compd. ^b	M.p./°C	Formula	Mol. weight		Anal.	Calc'd/Found/ ^a %		IR/cm ⁻¹		UV (ethanol)	
			Calc'd	Found ^c		C	H	$\nu_{C=O}^d$	$\nu_{C=C}$	λ_{max} nm	ϵ
(E)-I	93—6	C ₁₇ H ₁₆ FeO ₄	342.2	342	59.67 59.93	5.33 5.48	—	1700(s) ^e (broad)	1631(m)	247 294	11 500 12 300
(Z)-I	61—4	C ₁₇ H ₁₈ FeO ₄	342.2	342	—	—	—	1696(s) ^e (broad)	1626(m)	248 293	9200 10 800
(E)-II	oil	C ₁₈ H ₂₀ FeO ₄	356.2	—	60.70 60.76	5.66 5.35	—	1695(s) ^f 1736(s)	1634(s)	248 294	12 600 14 300
(Z)-II	oil	C ₁₈ H ₂₀ FeO ₄	356.2	356	—	—	—	1695(s) ^f 1735(s)	1634(m)	246 294	11 400 12 100
(E)-VI	70—3	C ₁₈ H ₂₀ FeO ₄	356.2	356	—	—	—	1700(s) ^f (broad)	1600(m)	236(sh) 281	10 500 8200
(Z)-VI	76—9	C ₁₈ H ₂₀ FeO ₄	356.2	356	—	—	—	1714(s) ^f (broad)	1598(m)	277	6700
(E)-VII	46—8	C ₁₉ H ₂₂ FeO ₄	370.2	—	61.64 61.35	5.99 6.05	—	1712(s) ^e 1740(s)	1603(m)	243 284	13 300 12 500
(Z)-VII	oil	C ₁₉ H ₂₂ FeO ₄	370.2	370	—	—	—	1700(s) ^e 1738(s)	1620(w)	234(sh) 282	10 900 8700
(E)-X	73—6	C ₂₄ H ₂₄ FeO ₄	432.3	—	66.68 66.70	5.60 5.42	—	1700(s) ^e 1734(s)	1615(m)	243 291	6400 4 000
(Z)-X	60—2	C ₂₄ H ₂₄ FeO ₄	432.3	—	66.68 66.48	5.60 5.36	—	1700(s) ^e 1735(s)	1608(m)	244 293	24 000 15 400

^a See Introduction to Experimental section;

^b Structural formulas are given in the Figure 1;

^c The overall yields of the reaction products I, VI and IX, resp., are 98, 90 and 91%, resp. The (E)- : (Z)-ratios are given in Theoretical part; mass spectra are given; the neutralization equivalents of the compounds I, VI and IX agreed within the limits of error with the calculated ones;

^d In the first row is given the frequency for the conjugated carbonyl group, and in the second row for the unconjugated carbonyl group (if two frequencies are resolved);

^e liquid film;

^f in CHCl₃.

TABLE II
 NMR Spectra^a

Compd. ^b	Ferrocene protons ^c				Side-chain protons											
	substituted ring				unsubstituted ring	CH ₃ CH ₂ O—	—CH ₂ —	CH ₃ O—	CH ₃ CH ₂ O—	—C=CR ^d						
	2-	5-	3-	4-							1'-	...	5'-			
(E)-II	4.36	4.60	m (4)	4.22	s (5)	1.34	t (3)	3.60	s (2)	3.77	s (3)	4.23	q (2)	7.63	s (1)
(Z)-II	4.30	4.55	m (4)	4.14	s (5)	1.46	t (3)	3.50	s (2)	4.08	s (3)	4.20	q (2)	7.53	s (1)
(E)-VII	4.30	4.40	m (4)	4.17	s (5)	1.28	t (3)	3.52	s (2)	3.68	s (3)	4.19	q (2)	2.52	s (3)
(Z)-VII	4.20	4.30	m (4)	4.13	s (5)	1.13	t (3)	3.44	s (2)	3.69	s (3)	4.13	q (2)	2.24	s (3)
(E)-X	4.25	t (2)	4.13	t (2)	4.04	s (5)	1.28	t (3)	4.05	s (2)	3.56	s (3)	4.00	q (2)	7.32	s (5)
(Z)-X	4.28	t (2)	4.18	t (2)	4.12	s (5)	1.28	t (3)	3.08	s (2)	3.75	s (3)	4.11	q (2)	7.39	s (5)

^a See introduction to Experimental section; s = singlet, t = triplet, q = quartet, m = multiplet; numerals in parentheses denote a number of protons;

^b See the footnote b of Table I;

^c The numerals refer to positions in substituted (2-through 5-) and unsubstituted ferrocene ring (1'-through 5'-);

^d II, R = H; VIII, R = Me; X, R = Ph.

(E)- α -Ferrocenylmethylenesuccinic Anhydride (V)

To a stirred solution of 4 ml trifluoroacetic anhydride in 25 ml of methylene chloride 314 mg (1 mmol) of dicarboxylic acid III was added at room temperature and stirring was continued for 1/2 hour. The reaction mixture was worked up in the usual way and purified by preparative TLC giving 157 mg (53%) of the analytical sample V; m.p. 138—40 °C. IR spectrum (KBr): 1835 (s), 1876 (s) ($\nu_{C=O}$) and 1636 cm^{-1} (s) ($\nu_{C=C}$); ^1H NMR spectrum: 3.47 (s, $-\text{CH}_2-$), 7.65 (s, $-\text{C}=\text{CH}$), ferrocene protons: 4.21 (s, unsubstituted ring) and 4.36—4.65 ppm (m, H_2-H_5).

Anal. $\text{C}_{15}\text{H}_{12}\text{FeO}_3$ (296.1) calc'd.: C 60.84; H 4.09%
found: C 60.76; H 4.31%

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SAŽETAK

Stobbe-ove kondenzacije acilferocena s dietilsukcinatom

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Stobbe-ovim kondenzacijama formil-, acetil- odn. benzoil-ferocena s dietilsukcinatom pripravljene su smjese (*E*)- i (*Z*)-stereoizomernih produkata, $\text{FcCR}=\text{C}(\text{CO}_2\text{Et})\text{CH}_2\text{CO}_2\text{H}$ ($\text{R}=\text{H}$, Me odn. Ph). Te su smjese razdijeljene kromatografskim postupcima u čiste spojeve, kojima je struktura određena na temelju spektroskopskih podataka.

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