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An Optically Active Ferrocene Carboxylic Acid

LARS WESTMAN* and KENNETH L. RINEHART, JR.

Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois, U.S.A.

Submitted in honour of the sixtieth birthday of Professor *Arne Fredga*

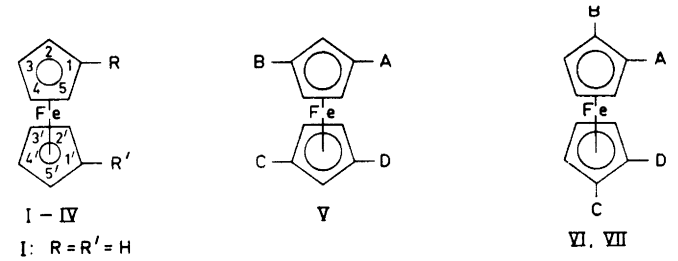
1,1′-Dimethylferrocene-2-carboxylic acid and 1,1′-dimethylferrocene-3-carboxylic acid have been separated by chromatography of their mixed *p*-bromobenzyl esters over alumina. The latter acid has been resolved by means of its cinchonidine salt, which gives the (+)-acid, and its quinidine salt, which gives the (−)-acid.

The geometry of ferrocene (I) [1] is unusual in that the two cyclopentadienyl rings are directly above one another, forming a "sandwich" [2] or "Doppelkegel" [3] structure. The unsubstituted nucleus is remarkably symmetrical, but with the introduction of substituents symmetry is lessened and in ferrocenes containing two or more substituents isomers are possible. Positional isomers were initially studied, by Woodward and Rosenblum [4], who acetylated ethylferrocene (II) to a mixture of 1′-, 2-, and 3-acetylethylferrocenes, and by Rinehart, Motz and Moon [5], who obtained mixtures of 2- and 3-acetyldialkylferrocenes from 1,1′-dimethyl- and 1,1′-diisopropyl-ferrocenes (III and IV, respectively). It has been pointed out by each of these groups, and elsewhere [1], that the number of such positional isomers obtained is precisely that predicted for a ferrocene molecule in which the energy barrier to rotation of the two rings with respect to one another is very low, and other evidence also has been accumulated [6] for ready rotation of the cyclopentadienyl rings.

With two or more substituents on each ring, geometrical isomers are possible as has been demonstrated by the isolation of *meso*- and (±)-forms of 3,3′-diacetyl-1,1′-dimethylferrocene (V) and 2,2′-diacetyl-1,1′-dimethylferrocene (VI) [7], and of 1,2; 1′,2′-*bis*-(α-ketotetramethylene)-ferrocene (VII) [8]. Again, the number of isomers obtained corresponds to the number expected for freely rotating rings.

Since the rings are free to rotate, the molecule does not differ greatly from ethane in its possibilities for optical isomerism. Thus, whenever there are at least two different substituents on one ring, optical isomers exist, just as in

* Present address: Glanshammarsgatan 45, Bandhagen 4, Sweden.



I – IV

I: R = R′ = H

II: R = C_2H_5, R′ = H

III: R = R′ = CH_3

IV: R = R′ = iso-C_3H_7

V

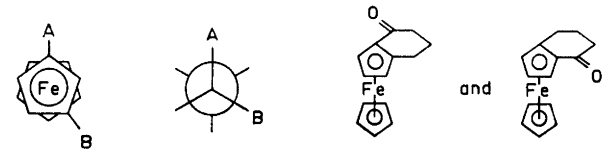
VI, VII

V and VI (*meso*): A = C = CH_3, B = D = $COCH_3$

(±): A = D = CH_3, B = C = $COCH_3$

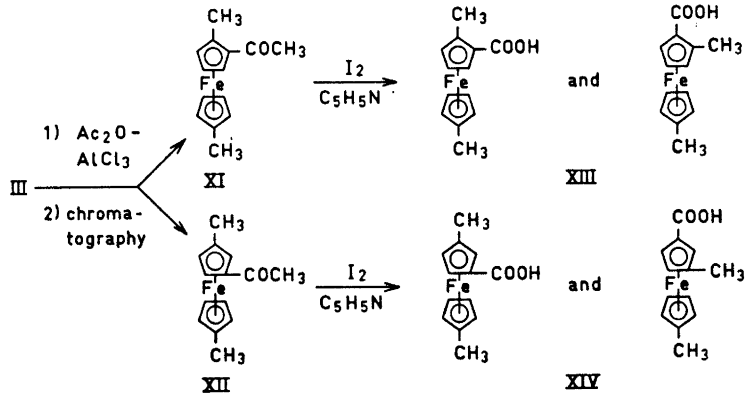
VII: A + B = C + D = $-(CH_2)_3CO-$

substituted ethanes optical isomers exist whenever one methyl group bears two different substituents (so long as neither of the two substituents is methyl). That this is so is seen by comparison of formulas VIII and IX.



VIII IX X

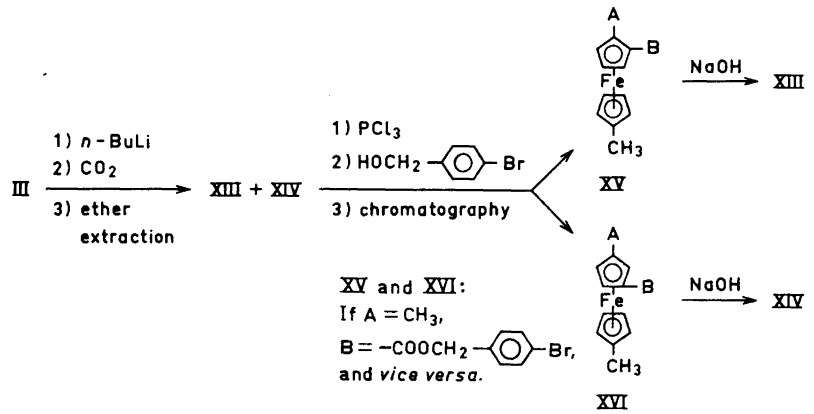
Optical isomers should, then, be obtainable for homoannularly disubstituted ferrocenes. This was first demonstrated by Thomson [9], who cyclized γ-ferrocenylbutyric acid to 1,2-α-ketotetramethyleneferrocene [8,10] and resolved the latter compounds by means of (−)-menthydrazide. The (+)-ketone obtained had $[\alpha]_D^{15}$ + 550° (*c* 0.3, $CHCl_3$), but the (−)-ketone was not isolated. The present work describes the first resolution of a trisubstituted ferrocene, 1,1′-dimethylferrocene-3-carboxylic acid (XIV), and, apparently, the only reported optically pure enantiomorphic ferrocene. It should be noted, however, that,



since the mono-substituted ring of XIV is free to rotate with respect to the disubstituted ring, no new element of asymmetry has been introduced beyond that of the 1,2-disubstituted compound X.

Both the 2- and 3-carboxylic acids from 1,1′-dimethylferrocene (XIII and XIV, respectively) were prepared earlier by hypoiodite oxidation of the corresponding 2-acetyl- and 3-acetyl-1,1′-dimethylferrocenes (XI and XII, respectively) [5]. The latter compounds, in turn, had been obtained by acetylation of 1,1′-dimethylferrocene (III) and separation on alumina of the isomeric ketones.

Since the hypoiodite oxidation step of the earlier reaction sequence gave low yields from the difficulty separable isomeric acetyldimethylferrocenes (XI and XII), an alternative route has been developed. In the present method [11] 1,1′-dimethylferrocene was treated with butyllithium * and then with carbon dioxide to give a mixture of acids, which was separated readily into mono- and di-carboxylic acids by the former's solubility and the latter's insolubility in ether [11]. Since earlier attempts to separate the 2- and 3-acids on ion exchange resins and their methyl esters on alumina had failed [11], the acids were converted to their more polar *p*-bromobenzyl esters. These proved readily separable on alumina and the esters XV and XVI were obtained in isomerically pure form. Saponification of these then gave the corresponding acids, which proved identical by melting points and infrared spectra to the acids obtained earlier from hypoiodite oxidation of the acetyl isomers [5]. Evidence for the positions of the acetyl groups in the latter compounds (XI and XII) includes their relative abundance (from acetylation, compared to the proportions of the corresponding acetyldiisopropylferrocenes obtained from acetylation) and their infrared spectra [5], their n.m.r. spectra [13], and their relation to dimethyldiethylferrocenes prepared by unambiguous routes, from ethylmethylcyclopentadienes [7,14].



Of the two isomers (XIII and XIV), the more abundant [11] 3-carboxylic acid was chosen for resolution, though resolution of the 2-isomer would pose no new problem beyond supply. A number of alkaloid salts of XIV were inves-

* Although Nesmeyanov, *et al.*, [12] reported that dimethylferrocene did not react with butyllithium, the reaction in fact appears to proceed quite facilely, [11] as noted in the text.

tigated. Cinchonidine and quinine precipitated preferentially the (+) isomer, and cinchonine, brucine, and quinidine the (−)-isomer, while strychnine gave no resolution at all (*cf.* Table 2). Of these, the cinchonidine and quinidine salts were chosen for further study since they gave acids of the highest absolute rotations. Each salt was recrystallized to constant melting point, then decomposed by acid to give the optical isomers. The (+)- and (−)-acids had the same melting point and equal, though opposite, rotation. Their properties are summarized in Table 1.

Table 1. Physical properties of 1,1′-dimethylferrocene monocarboxylic acids.

1,1′-Dimethylferrocene-	M.p.	$[\alpha]_D^{22}$ (*c* 0.8, $CHCl_3$)
(±)-2-carboxylic acid	123−126°	
(±)-3-carboxylic acid	108−109.5°	
(+)-3-carboxylic acid	119−121°	+ 37.5 ± 1.5°
(−)-3-carboxylic acid	119−121°	−36.0 ± 1.0°

EXPERIMENTAL

Melting points were determined on a Kofler micro hot-stage and are uncorrected. Rotations were determined on a Schmidt and Hænsch polarimeter, employing 1-dm cells.

Separation of 1,1′-dimethylferrocene-2-carboxylic and -3-carboxylic acids as their p-*bromobenzyl esters. Run I.* A mixture of 1,1′-dimethylferrocene-2-carboxylic and -3-carboxylic acids (11.6 g, 0.045 mole; obtained as the ether-soluble portion of the monoacid-diacid mixture from treatment of 1,1′-dimethylferrocene with butyllithium followed by carbon dioxide) [11] was mixed with 50 ml of benzene and 50 ml of phosphorus trichloride. The mixture was warmed briefly to dissolve the acids, left overnight at room temperature, finally heated for one hour at reflux, then cooled. The supernatant was decanted, solvent and excess phosphorus trichloride were removed under aspirator pressure. Two fresh 25-ml portions of benzene were added and aspirator evaporation was repeated after each addition.

The dark red residue was dissolved in 100 ml of benzene and 8.4 g (0.045 mole) of *p*-bromobenzyl alcohol in 100 ml of benzene was added. The mixture was warmed briefly on a steam bath, treated with charcoal, filtered and cooled. Ether (300 ml) was added and the solution was extracted four times with 50-ml portions of 5 % sodium bicarbonate, once with 50 ml of water, then dried over magnesium sulfate. Acidification of the bicarbonate solution gave 0.8 g. (7 % of recovered acids, while removal of benzene-ether solvent from the organic phase in a rotary evaporator yielded 17.3 g. (90 % conversion from acids, 96 % yield based on unrecovered acids) of crude ester.

This material, in benzene, was transferred to an alumina column (Merck, acid-washed, 3 cm × 110 cm). Benzene eluted two yellow bands from the column, while a third band remained at the top. Extrusion of the top of the column and extraction with ether and methanol gave 1.4 g of crude recovered acids, apparently formed by saponification on alumina. On evaporation of solvent from the first eluted band, 2.7 g of liquid α ester was obtained, while the second band yielded 5.7 g of solid β ester. An intermediate fraction was rechromatographed (2 × 67-cm column) to give an additional 1.0 g of liquid α ester (total: 3.7 g, 21 % yield, 19 % conversion) and 0.4 g of solid β ester (total: 6.1 g, 34 % yield, 32 % conversion).

A sample of the solid *p*-bromobenzyl 1,1′-dimethylferrocene-3-carboxylate was recrystallized from pentane; m.p. 57−58°. (Found: C 56.71; H 4.80. Calc. for $C_{20}H_{19}BrFeO_2$: C 56.25; H 4.47).

Run II. In a second run employing 1.0 g (0.004 mole) of mixed *a* and *β* mono-acids and 10 ml of phosphorus trichloride in 10 ml of benzene, the mixture stood for 20 h at room temperature, when solvent and excess phosphorus trichloride were removed and 0.75 g (0.005 mole) of *p*-bromobenzyl alcohol in 10 ml of benzene was added. Work-up as in Run I gave 0.10 g (10 %) of recovered acids and 1.6 g (quantitative) of crude esters. Chromatography (1.5 × 58-cm column, Merck acid-washed alumina, benzene eluant) gave 0.80 g (53 % yield, 48 % conversion) of the *a* ester, which did not crystallize during 2 months at deepfreeze temperature, and 0.68 g (46 % yield, 41 % conversion) of the *β* ester, m.p. 55—57° after recrystallization from pentane.

1,1'-Dimethylferrocene-2-carboxylic acid. The liquid *a* ester from Run I (3.7 g) was saponified during 1.5 h in refluxing aqueous alcoholic potassium hydroxide solution (2 g of alkali in 40 ml of ethanol and 10 ml of water). Water (50 ml) was added and most of the alcohol was removed in a rotary evaporator. Then, 50 ml more of water was added and the solution was extracted four times with 25-ml portions of ether. The combined ether extracts were washed twice with 15-ml portions of water which were combined with the main aqueous layer.

From the ether solution was recovered 1.6 g (quantitative) of crude *p*-bromobenzyl alcohol. Addition of 6 N hydrochloric acid to the basic solution precipitated 1,1'-dimethylferrocene-2-carboxylic acid, which was collected, washed with water and dried; 1.9 g (85 % yield from ester) of crude acid, m.p. 105—115°. Recrystallization from ether-pentane gave the analytical sample, m.p. 123—126° (lit.[5] m.p. 118—118.5°). (Found: C 60.54; H 5.48. Calc. for $C_{13}H_{14}FeO_2$: C 60.49; H 5.43).

The infrared spectrum of the acid is identical to that of an authentic sample [15]. The ultraviolet spectrum (absolute ethanol, 9.86×10^{-5} M) has λ_{max} 262 mμ, ε_{max} 5170.

The liquid ester from Run II (0.80 g) was saponified as in the preceding paragraph to yield 0.27 g (56 % yield) of 1,1'-dimethylferrocene-2-carboxylic acid, m.p. 117—122°. Solution in sodium bicarbonate, filtration, and reprecipitation with hydrochloric acid, followed by recrystallization from ether-pentane gave the pure acid, m.p. 122—125°.

1,1'-Dimethylferrocene-3-carboxylic acid. The solid *β* ester (6.1 g) from Run I above was saponified (4 g of potassium hydroxide in 120 ml of ethanol and 20 ml of water) as described for the *a* ester. Work-up as before gave 2.5 g (94 %) of recovered *p*-bromobenzyl alcohol and 3.2 g (87 % from ester) of crude acid, m.p. 105—108°. Recrystallization from ether-pentane gave the pure acid, m.p. 108—109.5° (lit.[5] m.p. 106—106.5°). (Found: C 60.23; H 5.54. Calc. for $C_{13}H_{14}FeO_2$: C 60.49; H 5.43).

The infrared spectrum of this acid was superimposable on that of authentic 1,1'-dimethylferrocene-3-carboxylic acid[15], while the ultraviolet spectrum (10.17×10^{-5} M, absolute ethanol) had λ_{max} 266 mμ, ε_{max} 5210.

In a second run a portion (0.30 g) of the solid *β* ester from Run II was saponified as in other runs to give 0.10 g (56 %) of crude acid, m.p. 95—105°, which was purified by solution in bicarbonate, filtration and reprecipitation with hydrochloric acid, then recrystallized from ether-pentane; m.p. 106—108°.

Table 2. Crystallization of alkaloid salts of 1,1'-dimethylferrocene-3-carboxylic acid.

Alkaloid (mg)	Crystallization 1st *a*	1st *b*	1st *c*	2nd *a*	2nd *b*	2nd *c*	3rd *a*	3rd *b*	3rd *c*	Acid *d*	Acid *e*	Acid *f*
Cinchonidine (294)	10	1	220	10	3	110				+30°	50	190
Quinine (378)	10	6	380	5	4	270	2	2	190	+15°	80	180
Strychnine (334)	7	6	420	5.5	4	230	2.5	2	180	0°	85	125
Cinchonine (294)	7	11	190	3	5	170				−10°	70	170
Brucine (466)	5	14	480	3	7	215				−21°	90	170
Quinidine (369)	8	5	300	5	3	160	3	2	130	−32°	60	160

[a] 95 % ethanol, ml. [b] Water, ml. [c] Salt collected, mg.
[d] Acid recovered from crystallized salts, $[\alpha]_D^{21}$ (c 1.0, in chloroform).
[e] Acid recovered from crystallized salts, mg. [f] Acid recovered from mother liquors, mg.

Optical resolution of 1,1'-dimethylferrocene-3-carboxylic acid. A. Preliminary experiments. Racemic 1,1'-dimethylferrocene-3-carboxylic acid (258 mg, 1.00 mmole) and 1.00 mmole of each of several alkaloids were dissolved in 95 % ethanol-water mixtures and set aside for crystallization. The salts obtained were recrystallized from ethanol-water, then decomposed to give the recovered ferrocene acid, which was tested for optical activity. The remainder of the acid was recovered from the mother liquors. Results are summarized in Table 2.

B. (+)-1,1'-Dimethylferrocene-3-carboxylic acid. Racemic 1,1'-dimethylferrocene-3-carboxylic acid (2.90 g, 0.011 mole, m.p. 108–109.5°) and 3.30 g (0.011 mole) of cinchonidine were dissolved in 90 ml of hot 95 % ethanol. Water (10 ml) was added and the solution was set aside. The cinchonidine salt, which crystallized in yellow needles, was collected, pressed and dried: yield, 3.08 g; m.p. 155–158°. Recrystallizations from ethanol-water are summarized in Table 3. (Found: C 69.47; H 6.46; N 4.86. Calc. for $C_{33}H_{36}FeN_2O_3$: C 69.56; H 6.57; N 5.07). The (+)-acid was obtained by decomposition of the salt with mineral acid.

Table 3. Recrystallizations of (+)-1,1'-dimethylferrocene-3-carboxylic acid cinchonidine salt

No.	95 % EtOH, ml	Water, ml	Salt isolated, g	Salt isolated, m.p.	Acid obtained m.p.	Acid obtained $[\alpha]_D^{22}$ (*c* 0.8, $CHCl_3$)
1	45	5	1.78	161 –164.5°		
2	27	3	1.27	164 –167°		+ 32°
3	18	2	1.02	168 –169.5°		
4	15	1.7	0.87	169 –171°		
5	15	1.7	0.75	168.5–171°	116.5–119°	+ 39°
6	15	1.7	0.47	169 –171°		
7	7.5	0.8	0.40	–		
8	7.5	0.8	0.34	169 –171°	119–121°	+ 36°

C. (−)-1,1'-Dimethylferrocene-3-carboxylic acid. Mother liquors from the initial crystallization and first recrystallization of the cinchonidine salt of the (+)-acid above were combined and acidified to give the crude (−)-acid (2.00 g), which was mixed with 2.86 g of quinidine and dissolved in 62 ml of hot 95 % ethanol. Water (38 ml) was added and the solution was set aside for crystallization. The precipitated salt was collected, pressed and dried: yield, 3.17 g; m.p. 108–115°. Recrystallizations from 95 % ethanol-water are summarized in Table 4. (Found: C 69.82; H 7.45; N 4.85. Calc. for $C_{33}H_{38}FeN_2O_4$: C 68.04; H 6.57; N 4.81.) The (−)-acid was liberated from the salt with mineral acid.

Table 4. Recrystallizations of (−)1,1'-dimethylferrocene-3-carboxylic acid quinidine salt.

No.	95 % EtOH, ml	Water, ml	Salt isolated, g	Salt isolated, m.p.	Acid obtained, m.p.	Acid obtained, $[\alpha]_D^{22}$ (*c* 0.8, $CHCl_3$)
1	50	25	2.22	113–120°		
2	35	17.5	1.82		112–117°	−35°
3	30	15	1.30			
4	30	15	0.95			
5	25	8	0.75	118–122°	119–121°	−37°

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