

## Spiroferrocenophanes

### II\*. Grignard addition and reduction reactions of spiro[5]ferrocenophane-3,1'-cyclohexane-1,5-dione

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(Received August 10th, 1989)

#### Abstract

Reactions of spiro[5]ferrocenophane-3,1'-cyclohexane-1,5-dione with Grignard reagents give the corresponding 1-hydroxy-5-ones and/or 1,5-dihydroxy derivatives, though there is a competing reduction of the carbonyl groups in the starting material by alkylmagnesium halides possessing  $\beta$ -hydrogen atoms. The dihydroxy derivatives with one or two hydrogen atoms introduced at positions 1 and/or 5 appeared to be highly unstable, undergoing spontaneous dehydration to the corresponding ethers. Detailed analysis of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the compounds obtained revealed complete rigidity of the ferrocenophane bridge.

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#### Introduction

We have reported [2] that the reaction of 3-aryl[5]-ferrocenophane-1,5-diones with alkylmagnesium reagents gives two isomeric 1-alkyl-1-hydroxy-3-aryl[5]ferrocenophane-5-ones and only one 1,5-dialkyl-1,5-dihydroxy-3-aryl[5]ferrocenophane. The hydroketones exist in two different stable conformations, with a chair shape or twisted bridge.

It was interesting to make a comparison between the reactions of Grignard reagents with the newly synthesized spiro[5]ferrocenophane-3,1'-cyclohexane-1,5-dione [1], and with the 3-aryl- or 3-alkyl-[5]ferrocenophane-1,5-diones described previously [2]. This time, careful separation of the product mixtures allowed isolation and identification of both the main and the side products.

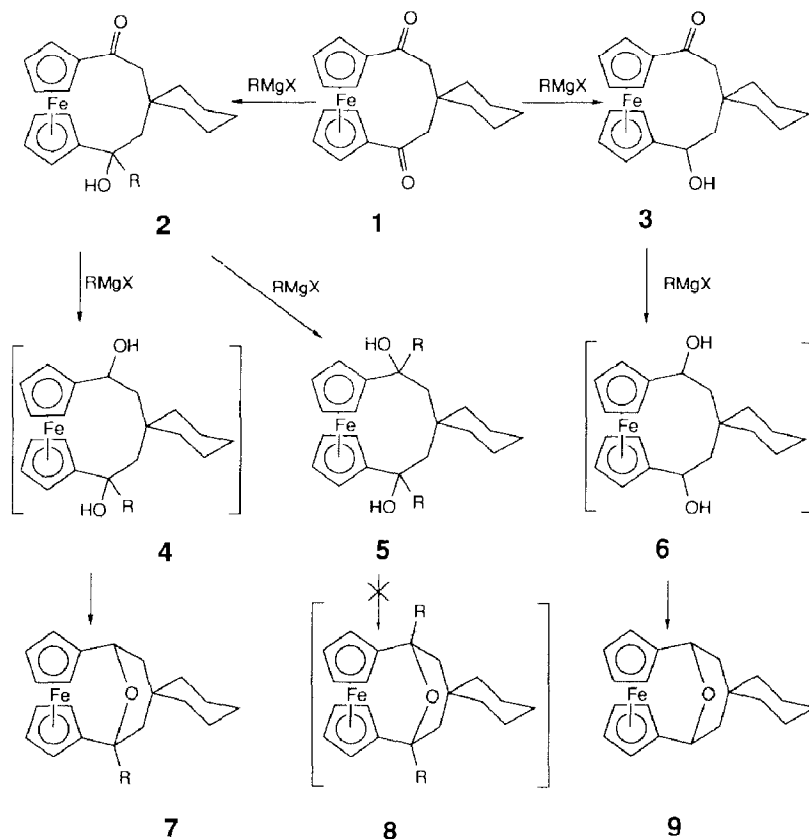
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\* For part 1 see ref. 1.

## Results and discussion

A suspension of spiro[5]ferrocenophane-3,1'-cyclohexane-1,5-dione (**1**) in dry ether was treated with an excess of alkylmagnesium halide. It was immediately obvious that the carbonyl groups of **1** are much less reactive than those of the [5]ferrocenophanes investigated previously [2]. The starting ketone **1** remained in the mixture even after 24 h stirring with a threefold excess of the alkylmagnesium halide. The only exception was with in the reaction involving methylmagnesium chloride, which under the same conditions did not leave any unchanged starting ketone. This indicates that the lower reactivity of the investigated spiroferrocenophanedione **1** is due to steric hindrance around its carbonyl groups. Hydroxyketone **2** (Scheme 1), expected to be the main product, could be obtained in satisfactory yield (68%) only from the reaction of **1** with methylmagnesium chloride. Unexpectedly, Grignard reduction to hydroxyketone **3** appeared to compete successfully with the Grignard addition.

Comparison of the Grignard addition and reduction mechanisms [3,4] leads to the conclusion that significant reduction will occur only when there is a strong steric hindrance around the carbonyl group of the ketone and when the magnesium reagent possesses at least one  $\beta$ -hydrogen atom. The six-center process involves loss of the  $\beta$ -hydrogen atom with a pair of electrons, which is easier when there is an



Scheme 1

Table 1

Reaction conditions, separation methods, and yields of products

RMgX	Reaction time (h)	RMgX/1 ratio	Separation method <sup>a</sup>	Yields (%)					
				1	2	3	5	7	9
MeMgCl	24	4/1	a	0	68	0	0	0	0
MeMgI	24	10/1	b	10	17	0	4	0	0
EtMgI	24	10/1	c	0	39	0	0	0	0
i-PrMgI	40	10/1	b	3	15	14	7	0	0
i-BuMgI	24	3/1	b	16	6	13	0	1	2
i-BuMgI	24	10/1	b	0	16	14	0	0	0
t-BuMgBr	24	10/1	b	50	6	0	0	0	0
t-BuMgCl	120	12/1	b	29	16	0	0	0	0
t-BuMgCl	2500	10/1	b	34	19	0	0	0	0
PhCH <sub>2</sub> MgCl	24	4/1	b	0	52	0	17	0	0
PhMgBr	24	4/1	b	12	24	0	40	0	0

<sup>a</sup> (a) Recrystallization from benzene-cyclohexane, (b) chromatography on silica gel. (c) recrystallization from n-hexane.

electron donating alkyl group on the  $\beta$ -carbon atom. Thus the ethylmagnesium reagents are less effective as reducing agents than corresponding species with longer carbon chains [3]. On the other hand, two molecules of alkylmagnesium halide are involved in the transition state leading to the addition product which means that much more room is needed around the carbonyl group and so the reaction is disfavored by bulky Grignard reagents.

In our hands, reaction of dione **1** with a large excess of ethylmagnesium iodide (molar ratio 10/1) afforded hydroxyketone **2b** in a comparatively good yield (39%). A similar reaction of **1** with isobutylmagnesium iodide gave the corresponding hydroxyketone, **2d**, in only 16% yield, and a relatively high yield of hydroxyketone **3** (14%) (Table 1). When the molar ratio of the reagents was lower or the reaction time shorter, the reaction was slower and starting dione **1** was usually isolated from the reaction mixture. Reaction of **1** with t-butylmagnesium reagents gave **2e** as the only product, but the starting material appeared to be the dominant component in the reaction mixtures even when the reaction was carried for 2500 h.

Reduction of the spirodione **1** with sodium borohydride was found to show the some features as the Grignard reaction, the reduction stopped at hydroxyketone **3**, which could be separated in a good yield.

The observations noted above indicate that the behavior of the spiro derivatives of [5]ferrocenophane-1,5-dione in Grignard reactions and reductions with sodium borohydride is quite different from that of the 3-aryl or 3-alkyl derivatives of the same dione [2] previously reported. Only one isomer of hydroxyketone **2** was formed in the reactions reported here, whereas two isomers were observed in the previous work.

The second difference observed between the [5]ferrocenophane-1,5-diones mono-substituted at C(3) and those involving a spiro system at the same carbon atom was in the rates of the Grignard addition to the carbonyl groups. The reactions were much more slower in the case of the spiro derivative. This can be attributed to the strain in the bridge and the steric hindrance introduced by the spiro system. The

hindrance around the carbonyl group favors the Grignard reduction, and so the products of type **3** are often important components of the product mixtures.

The last observed difference is in the ease of formation of bridged ethers **7** and **9** by spontaneous dehydration of the appropriate diols formed by reduction of the hydroxyketones **2** and **3**. Formation of such tetrahydropyran rings was reported [5] previously in the reduction of unsubstituted [5]ferrocenophane-1,5-dione and its 3-phenyl derivative, but was not observed in our Grignard reactions [2] of 3-substituted [5]ferrocenophane-1,5-diones. In contrast to **4** and **6**, diols **5** have been

Table 2

Analyses, melting points, recrystallization solvents, and IR data for the various products

Compound	R		Analysis (Found (Calcd.) (%))		M.p (°C)	Solvent	IR	
			C	H			$\nu(\text{C=O})$ (cm <sup>-1</sup> )	$\nu(\text{O-H})$ (cm <sup>-1</sup> )
<b>2a</b>	Me	C <sub>21</sub> H <sub>26</sub> FeO <sub>2</sub>	69.2 (68.9)	7.1 (7.2)	159	toluene	1630	3460
<b>2b</b>	Et	C <sub>22</sub> H <sub>28</sub> FeO <sub>2</sub>	69.6 (69.5)	7.6 (7.4)	152	n-hexane	1633	3470
<b>2c</b>	i-Pr	C <sub>23</sub> H <sub>30</sub> FeO <sub>2</sub>	70.0 (70.1)	7.5 (7.7)	157	n-hexane	1638	3441
<b>2d</b>	i-Bu	C <sub>24</sub> H <sub>32</sub> FeO <sub>2</sub>	71.0 (70.6)	7.5 (7.9)	164	n-hexane	1622	3499
<b>2e</b>	t-Bu	C <sub>24</sub> H <sub>32</sub> FeO <sub>2</sub>	70.5 (70.6)	7.4 (7.9)	219	n-hexane/ benzene (4/1)	1620	3529
<b>2f</b>	PhCH <sub>2</sub>	C <sub>27</sub> H <sub>30</sub> FeO <sub>2</sub>	73.6 (73.3)	7.0 (6.8)	166	n-hexane/ benzene (15/1)	1630	3516
<b>2g</b>	Ph	C <sub>26</sub> H <sub>28</sub> FeO <sub>2</sub>	73.1 (72.9)	6.8 (6.6)	184	toluene	1625	3510
<b>3</b>	-	C <sub>20</sub> H <sub>24</sub> FeO <sub>2</sub>	68.2 (68.2)	6.6 (6.9)	155	toluene	1644	3418
<b>5a</b>	Me	C <sub>22</sub> H <sub>30</sub> FeO <sub>2</sub>	69.0 (69.1)	7.7 (7.9)	157	n-hexane/ toluene (4/1)	-	3232 3364
<b>5b</b> <sup>a</sup>	Et	C <sub>24</sub> H <sub>34</sub> FeO <sub>2</sub>	70.0 (70.2)	8.5 (8.4)	171	THF/water (5/1)	-	3240 3380
<b>5c</b>	i-Pr	C <sub>26</sub> H <sub>38</sub> FeO <sub>2</sub>	71.0 (71.2)	8.5 (8.7)	196	ether	-	3241 3402
<b>5f</b>	PhCH <sub>2</sub>	C <sub>34</sub> H <sub>38</sub> FeO <sub>2</sub>	76.3 (76.4)	7.6 (7.2)	155	n-hexane/ benzene (4/1)	-	3283 3396
<b>5g</b>	Ph	C <sub>32</sub> H <sub>34</sub> FeO <sub>2</sub>	76.1 (75.9)	6.8 (6.8)	196	toluene	-	3187 3367
<b>7d</b>	i-Bu	C <sub>24</sub> H <sub>32</sub> FeO	73.5 (73.5)	8.8 (8.2)	164	n-hexane	-	-
<b>7f</b> <sup>b</sup>	PhCH <sub>2</sub>	C <sub>27</sub> H <sub>30</sub> FeO	76.4 (76.1)	7.8 (7.1)	172	n-hexane	-	-
<b>9</b>	-	C <sub>20</sub> H <sub>24</sub> FeO	71.2 (71.4)	7.2 (7.2)	188	n-hexane	-	-

<sup>a</sup> Obtained from reaction of **2b** with ethylmagnesium iodide. <sup>b</sup> Obtained by reduction of **2f** with sodium borohydride.

found to be quite stable, and corresponding ethers **8** were never isolated or even detected in the reaction mixtures. Data for the products obtained are listed in Table 2.

### Spectra and structure of hydroxyketones **2** and **3**

The IR spectrum of a highly dilute solution of **2b** (0.002 *M* in carbon tetrachloride) showed a hydroxyl stretching band at  $3510\text{ cm}^{-1}$ . The position of this band, comparable with those for  $\gamma$ -hydroxyketones [6] and 1-acetyl-1'-( $\alpha$ -hydroxyethyl) ferrocene [7] is evidence of intramolecular hydrogen bonding between the hydroxyl and carbonyl groups. Dreiding molecular models of hydroxyketones **2** revealed that for hydrogen bonding the molecule must be chair shape, with the R groups directed equatorially relative to the bridge and axially relative to the cyclopentadienyl rings (Fig. 1). Each pair of the bridge methylene hydrogen atoms, on C(2) and C(4), consists of an equatorial ( $H^e$ ) and an axial ( $H^a$ ) hydrogen atom.

Two downfield shifted multiplets, at  $\delta$  4.91 and 4.72 ppm (Table 3), in the  $^1\text{H}$  NMR spectrum of **2a** can be attributed to two  $\beta$ -cyclopentadienyl hydrogen atoms on the ring attached to the carbonyl group. The most deshielded proton is located *syn* and the other *anti* to the carbonyl group. Two independent resonances of the protons indicate that there is no rotation of the carbonyl group on the NMR scale time. The multiplets mentioned are accompanied by a two-proton multiplet at  $\delta$  4.55 ppm, arising from the  $\gamma$  protons of the same ring. (The latter assignment was based on a comparison of the spectrum with that of glycol **5a**; the signals of the protons on the cyclopentadienyl ring adjacent to the carbinol carbon atom are shifted further upfield.) The remaining two signals, a one-proton multiplet at  $\delta$  4.40

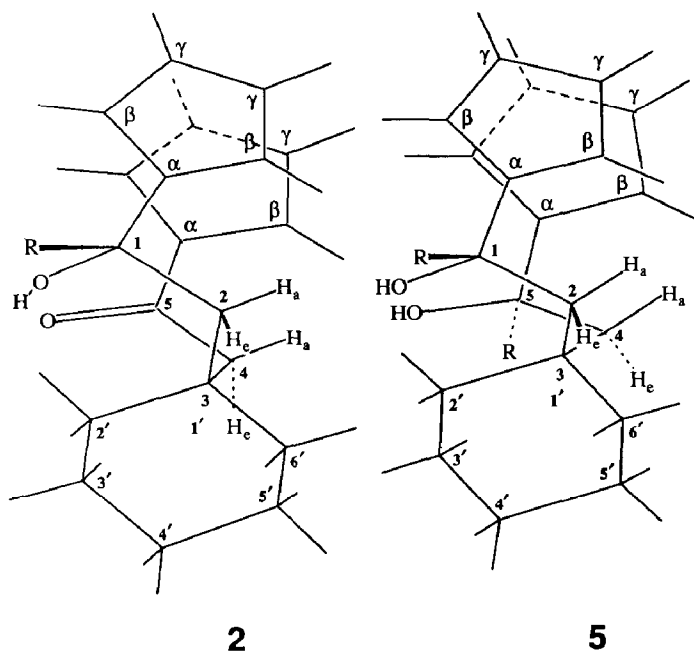


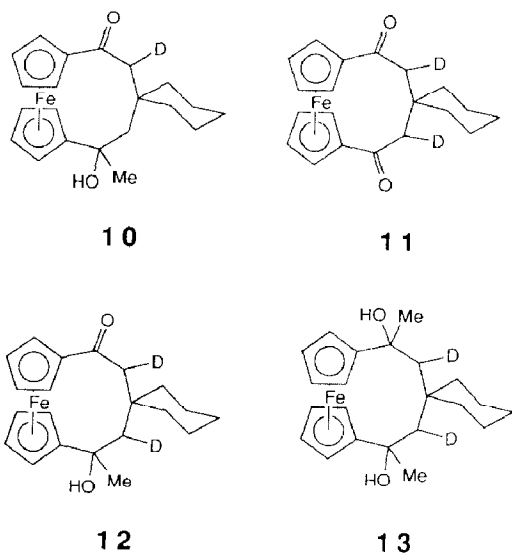
Fig. 1. Molecular models of hydroxyketones **2** and diols **5**.

Table 3

	Cyclopentadienyls	C(2)H <sub>2</sub>	C(4)H <sub>2</sub>	Substituents	Cyclohexane ring	Others
<b>2a</b>	4.15m(3H), 4.40m(1H), 4.55m(2H), 4.72m(1H) 4.91m(1H)	1.88s(2H)	2.67d(1H,14.1) 2.89d(1H,14.1)	1.31s(3H)	1.55m(10H)	2.54s(1H,OH)
<b>2b</b>	4.12m(3H), 4.36m(1H) 4.56m(2H), 4.73m(1H) 4.90m(1H)	1.78s(2H)	2.59d(1H,14.1) 2.95d(1H,14.1)	0.67t(3H,7.0) 1.51qt(2H,7.0)	1.62m(10H)	2.43s(1H,OH)
<b>2c</b>	4.10m(2H), 4.17m(1H), 4.33m(1H), 4.55m(2H), 4.74m(1H), 4.87m(1H)	1.68m(2H)	2.59d(1H,14.1) 2.98d(1H,14.1)	0.63d(3H,6.6) 0.80d(3H,6.6) <sup>b</sup>	1.56m(10H)	2.38s(1H,OH)
<b>2d</b>	4.10m(2H), 4.19m(1H), 4.39m(1H), 4.54m(2H), 4.74m(1H), 4.88m(1H)	1.82(2H,s)	2.58d(1H,14.1) 2.95d(1H,14.1)	0.72d(6H,5.16) <sup>b</sup>	1.55m(10H)	2.33s(1H,OH)
<b>2e</b>	4.08m(2H), 4.22m(1H), 4.39m(1H), 4.47m(1H), 4.54m(2H), 4.86m(1H)	1.31d(1H,12.7) 1.75d(1H,12.7)	2.61d(1H,13.6) 3.01d(1H,13.6)	0.78s(9H)	1.57m(10H)	2.18s(1H,OH)
<b>2f</b>	3.96m(3H), 4.13m(1H), 4.48m(2H), 4.69m(1H), 4.81m(1H)	1.73d(1H,15.0) 1.99d(1H,15.0)	2.56d(1H,14.1) 2.95d(1H,14.1)	2.74m(2H) 6.85m(2H) 7.13m(3H)	1.49m(10H)	2.49s(1H,OH)
<b>2g</b>	4.17m(1H), 4.30m(2H), 4.36m(1H), 4.50m(2H) 4.78m(2H)	1.93m(2H)	2.32d(1H,15.5) 2.48d(1H,15.5)	7.08m(3H) 7.25m(2H)	1.34m(5H) 1.51m(5H)	2.47s(1H,OH)
<b>3</b>	4.14m(1H), 4.20m(1H), 4.30m(1H), 4.37m(1H), 4.49m(2H), 4.64m(1H), 4.47m(1H)	1.82(dd,1.9 and 15.0) 2.05(dd,10.3 and 15.0)	2.31d(1H,13.2) 2.46d(1H,13.2)	-	1.54m(10H)	4.55m(1H, C(5)-H)

<b>5a</b>	3.89m(2H), 4.12m(4H), 4.28m(2H)	1.93d(2H,15.5) 2.10d(2H,15.5)	1.93d(2H,15.5) 2.10d(2H,15.5)	1.41s(6H)	1.26m(2H) 1.53m(6H) 2.13m(2H)	4.66bs(2H,OH)
<b>5b</b>	3.88m(2H), 4.12m(4H) 4.25m(2H)	1.79d(2H,14.9) 2.05d(2H,14.9)	1.79d(2H,14.9) 2.05d(2H,14.9)	0.69t(6H,7.3) 1.60q(4H,7.3)	1.28m(2H) 1.48m(2H) 1.58m(4H) 2.15m(2H)	4.43bs(2H,OH)
<b>5c</b>	3.90m(2H), 4.11m(4H) 4.26m(2H)	1.62d(2H,15.0) 2.11d(2H,15.0)	1.62d(2H,15.0) 2.11d(2H,15.0)	0.68d(6H,6.6) 0.82d(6H,6.6) <sup>b</sup>	1.54m(6H) 1.38m(2H) 2.13m(2H)	4.73s(2H,OH)
<b>5f</b>	3.77m(2H), 3.91m(2H) 4.00m(2H), 4.08m(2H)	1.75d(2H,15.0) 2.22d(2H,15.0)	1.75d(2H,15.0) 2.22d(2H,15.0)	2.81s(2H) 6.86m(2H) 7.14m(3H)	1.27m(6H) 1.43m(2H) 1.86m(2H)	4.34s(2H,OH)
<b>5g</b>	4.18m(2H), 4.30m(6H)	2.35d(2H,15.5) 2.45d(2H,15.5)	2.35d(2H,15.5) 2.45d(2H,15.5)	7.00-7.45 m(10H)	1.35m(8H) 1.56m(2H)	5.62s(2H,OH)
<b>7d</b>	4.06m(2H), 4.16m(5H), 4.27m(1H)	1.60-2.20(m)	1.60-2.20(m)	0.70d(3H,6.1) <sup>b</sup> 0.93d(3H,6.1)	1.10-1.70 m(10H)	4.57dd(1H, 6.6 and 9.9, C(5)-H)
<b>7f</b>	4.05m(3H), 4.25m(5H)	1.80-2.30(m)	1.80-2.30(m)	3.14s(2H) 7.13bs(5H)	1.15-1.80 m(10H)	4.65dd(1H, 7.0 and 9.9, C(5)-H)
<b>9</b>	4.08d(2H,2.3 and 1.6), 4.16m(4H), 4.24dt(2H,2.5 and 1.2)	1.34dd(1H, 6.6 and 13.2) 2.10dd(1H, 9.7 and 13.2)	1.34dd(1H, 6.6 and 13.2) 2.10dd(1H, 9.7 and 13.2)	-	1.30m(2H) 1.50m(6H) 1.87m(2H)	4.55 dd(2H, 6.6 and 9.7, C(1)-H and C(5)-H)

<sup>a</sup> Chemical shifts are in ppm and coupling constants (in parentheses) in Hz. <sup>b</sup> Part of the substituent signals is overlapped by multiplets from the cyclohexane ring protons.



ppm and a three-proton multiplet at  $\delta$  4.12 ppm, must be assigned to the second cyclopentadienyl ring adjacent to the carbinol carbon atom. The signal from one  $\beta$ -proton on the carbinol side ring seems to be from that lying close to the hydroxyl group (Fig. 1).

The singlet at  $\delta$  2.54 ppm disappeared when tetradeuteriomethanol was added to the solution of **2a** in deuteriochloroform, indicating that it arises from the OH group. A pair of doublets at  $\delta$  2.89 and 2.67 ppm ( $J$  14.1 Hz) was assigned to the C(4) methylene group. Two individual signals of the methylene group protons indicate that this part of the molecule is inflexible, providing further confirmation of the presence of strong intramolecular hydrogen bonding.

To confirm this assignment, the 4-deuterio derivative **10** was obtained by stirring under reflux a mixture of a dioxane solution of **2a** with one of potassium deuteriooxide in deuterium oxide. Surprisingly, one of the doublets, at lower field, disappeared almost completely, whereas the second changed into a broadened singlet. Although the integral of that singlet indicated less than one proton, it is apparent that the rates of deuterium exchange of the methylene group protons are different. This observation strongly supports the previous finding that this part of the bridge is rigid. Proton  $H^a$  at C(4) of **2**, because of its location between the cyclopentadienyl and cyclohexane rings, is protected from attacks by the deuterioxide anion.

Next in the spectrum of **2a** comes a singlet at  $\delta$  1.88, which can be assigned to two C(2) methylene protons, even though two doublets would be expected. To prove validity of this assignment, deuterium labelled derivative **12** was synthesized by reaction of deuterioferrocenophanodion (**11**) with methylmagnesium iodide. Its spectrum showed a singlet with the same shift as **2a** but of much lower intensity. The remaining two signals can be easily assigned. A multiplet centered at  $\delta$  1.55 arises from resonances of the cyclohexane ring protons and a singlet at  $\delta$  1.31 arises from the methyl group protons.

Assignments of the spectra for all other hydroxyketones **2** and hydroxyketone **3** were based on those given for **2a**. The  $^1H$  NMR data are listed in Table 3.



Investigation of substituent effects on the spectra may provide further information about the molecular structure.

All the hydroxyketones **2** give a sharp singlet due to the hydroxy proton, and provide additional evidence for strong intramolecular hydrogen bonding. The OH resonance of **3** is broad and overlaps with other signals, which means that its exact chemical shift cannot be given. In this case, probably intermolecular hydrogen bonding can also occur.

A dramatic change is observed in the C(2) methylene group resonances. Two sets of doublet of doublets resulted from independent resonances of the C(2) protons and their splitting by the C(1) proton observed in the spectrum of **3**, changed into a singlet after substitution of the proton on C(1) by a methyl or an ethyl group (**2a** or **2b**). The singlet broadened when the substituent was isopropyl, and again split into a set of two doublets when the C(1) proton was replaced by a t-butyl (**2e**) or benzyl (**2f**) group. In the last case, diamagnetic anisotropy of the phenyl ring seems to be responsible for the difference between the methylene proton resonances, but in the case of **2e** it may result from an additional rigidity of the bridge caused by the bulky substituent.

The pattern of the ferrocene proton resonances is of interest. In the case of **3**, all the protons on the ring adjacent to C(1) have different shifts, giving four independent multiplets, at  $\delta$  4.14, 4.20, 4.30, and 4.37 ppm. The pattern changes, however, when the C(1) proton is replaced by an alkyl group. In the spectra of methyl and ethyl derivatives, **2a** and **2b**, one multiplet is observed for 3 protons, but in the case of the isopropyl and t-butyl derivatives, **2c** and **2e**, one proton multiplet more is observed. The influence of the substituents on C(1) on the proton resonances of the second cyclopentadienyl ring is weaker, except in the case of the phenyl substituent.

Shifts of the methyl group resonances in the spectra of **2b–2e** to a relatively higher field indicate that these groups lie within the shielding cone of the ferrocene moiety [8,9]. This means that the substituents are directed axially relative to the cyclopentadienyl ring, outside the space enclosed by the cyclopentadienyl planes. This confirms the chair conformation of the bridge in hydroxyketones **2**.

Off-resonance decoupled  $^{13}\text{C}$  NMR spectrum of **2b** revealed two peaks of the cyclopentadienyl quaternary carbon atoms, at  $\delta$  80.87 and 97.90 ppm, which were assigned to the cyclopentadienyl  $\alpha$ -atoms, C(5) and C(1), respectively. The first shift agrees well with that for the ferrocenyl carbon atom adjacent to the carbonyl group observed [1] in the spectrum of spirodione **1** ( $\delta$  80.57 ppm). The signal at  $\delta$  207.11 ppm in the spectrum of **2b** is characteristic of the carbonyl group. The analogous signal for **1** was at  $\delta$  203.67 ppm. Two other quaternary carbon peaks observed in the spectrum, at  $\delta$  74.82 and 39.56 ppm, are attributable to C(1) and C(3), respectively. A quartet in the off resonance spectrum of **2b** at  $\delta$  8.26 ppm arises from the methyl group of the ethyl substituent.

Further assignments could be made by examination of the spectra of deuterated species **10** and **12**. Disappearance of the peak at  $\delta$  44.0 ppm in the spectrum of **10** and the peaks at  $\delta$  44.0 and 49.5 in the spectrum of **12** indicates resonances that arise from C(4) and C(2), respectively. The remaining methylene resonances were assigned to the cyclohexane ring carbons. As can be seen from Table 4, the positions of these signals are almost insensitive to the substituents on C(1).

The off-resonance  $^{13}\text{C}$  NMR spectrum of **3** allowed recognition of the signal from C(3) as the highest field singlet at  $\delta$  38.8 ppm. The remaining singlets, at  $\delta$

Table 4. Carbon-13 chemical shift data for the various products (in ppm)

Compound	C( $\alpha$ )	C( $\beta$ ) and C( $\gamma$ )	C(1)	C(2)	C(3)	C(4)	C(5)	Substituents	Cyclohexane ring methylenes
<b>2a</b>	80.9 99.6	65.7, 66.8, 69.4, 69.8 69.6, 70.3, 73.6, 73.8	72.8	49.5	39.5	44.0	206.9	15.7	21.9, 21.9, 26.3, 37.0, 41.9
<b>2b</b>	80.9 97.9	66.6, 68.0, 69.1, 69.9 70.1, 70.2, 73.6, 73.9	75.1	47.7	39.7	43.9	207.1	8.4, 44.5	21.9, 22.0, 26.4, 37.0, 41.9
<b>2c</b>	81.1 97.2	67.0, 68.8, 69.4, 69.7 69.9, 70.3, 73.5, 73.8	76.1	45.0	40.0	44.9	206.9	17.2, 17.4, 44.9	21.9, 22.0, 26.4, 37.3, 41.4
<b>2d</b>	81.1 99.0	66.7, 68.1, 69.0, 70.0 70.1, 70.2, 73.4, 73.7	75.2	48.6	39.7	43.9	207.0	23.8, 24.5, 24.7, 60.5	21.9, 21.9, 26.3, 37.0, 41.7
<b>2e</b>	81.5 96.8	67.6, 68.5, 69.5, 69.6, 70.0, 70.4, 73.3, 73.4	78.9	45.0	40.2	41.4	207.0	25.4, 41.0	21.7, 21.8, 26.3 36.9, 41.4
<b>2f</b>	81.2 97.9	67.1, 68.1, 68.7, 69.8 70.0, 70.3, 73.3, 73.6	75.0	47.1	39.6	43.9	206.6	57.2, 126.3, 127.4, 131.0, 136.7	21.8, 21.8, 26.3, 37.0, 41.4
<b>2g</b>	80.6 100.1	65.5, 67.1, 68.2, 68.3, 71.0, 71.1, 74.1, 74.2	76.2	52.1	40.5	46.0	203.8	124.3, 125.9, 127.9, 153.2	22.0, 22.1, 26.0 38.5, 44.6
<b>3</b>	81.8 91.0	67.0, 70.1, 70.2, 70.3 70.4, 70.7, 73.0, 73.2	65.6	46.0	38.8	45.3	204.2	--	21.7, 21.8, 26.4, 34.3, 39.6
<b>5a</b>	100.8	64.7, 65.5, 67.5, 67.9	72.0	50.3	39.0	50.3	72.0	40.1	22.2, 22.3, 26.6, 36.7, 45.9
<b>5b</b>	98.6	65.5, 66.4, 67.4, 67.7	74.3	48.7	38.7	48.7	74.3	8.8, 43.8	22.2, 22.3, 26.6 36.3, 46.5
<b>5c</b>	96.6	66.0, 67.2, 67.3, 67.4	76.2	46.1	38.7	46.1	76.2	17.4, 17.8, 44.3,	22.1, 22.4, 26.6 35.7, 47.2
<b>5f</b>	98.6	65.7, 66.3, 67.3 67.9	74.2	48.4	38.6	48.4	74.2	56.4, 126.3, 127.5 131.0, 137.0	21.6, 22.1, 26.3 35.6, 46.4
<b>5g</b>	100.2	65.5, 67.2, 68.2 68.3	76.2	52.1	40.5	52.1	76.2	124.3, 126.0, 127.9, 153.1	22.1, 22.2, 26.3, 36.6, 46.1
<b>7f</b>	90.7 93.3	67.8, 68.5, 68.8, 69.6 70.0, 70.3, 71.0, 71.5	70.1	40.1	33.5	35.9	63.3	49.0, 126.3, 127.7, 131.2, 137.6	22.0, 22.4, 26.6, 35.6, 42.6
<b>9</b>	89.1	68.5, 69.7, 70.0, 70.7	61.6	36.4	32.4	36.4	61.6	--	21.8, 22.3, 26.5 35.2, 42.0
<b>10</b>	80.8 99.6	65.8, 66.8, 69.4, 69.8 69.9, 70.3, 73.6, 73.8	72.9	49.5	39.4	--	207.0	15.7	21.8, 21.8, 26.2, 36.9, 41.7
<b>12</b>	80.8 99.6	65.8, 66.8, 69.4, 69.8 69.9, 70.4, 73.6, 73.8	72.7	--	39.3	--	207.0	15.7	21.8, 21.8, 26.2 36.9, 41.9
<b>13</b>	100.8	64.7, 65.5, 67.5, 67.9	72.0	--	40.0	--	72.0	40.1	22.2, 22.3, 26.6, 36.6, 45.8

81.8, 91.0 and 204.2 ppm, in the same spectrum were readily assigned to C( $\alpha$ ) at C=O, C( $\alpha$ ) at CH-OH and the carbonyl group, respectively. The highest field doublet arising in this spectrum at  $\delta$  65.6 ppm was assigned to the resonance of C(1). Comparison of the spectrum of **3** with that of **2a** all identification of the resonances of the cyclohexane methylene groups. Two remaining methylene group signals, at  $\delta$  45.3 and 46.0 ppm, were assigned to the bridge C(4) and C(2) atoms, respectively. The upfield shift of the C(2) signal of **2a** (+3.5 ppm) relative to that for **3** reflects the  $\beta$ -effect of the methyl group [10,11].

### Spectroscopy and structure of glycols **5**

Dreiding models of the molecules of glycols **5** (Fig. 1) revealed that presence of hydrogen bonding between the hydroxyl groups requires the bridge to be "chair" shape and the substituents R directed out of the space enclosed between the cyclopentadienyl ring planes. The bridge methylene hydrogen atoms can be divided into two groups; hydrogens H<sup>a</sup>, cis to substituents R, lie in the cyclopentadienyl ring planes, and hydrogens H<sup>c</sup>, trans to R, lie outside the space enclosed between the cyclopentadienyl ring planes.

The <sup>1</sup>H NMR spectra of glycols **5** are consistent with the structural indications derived from Dreiding models. The spectrum of **5a** exhibits a pair of doublets, at 2.10 and 1.93 ppm, with coupling constants of 15.5 Hz, which can be assigned to the H<sup>a</sup> and H<sup>c</sup> protons, respectively (reflecting the deshielding effect of the ferrocene moiety [8]). The cyclopentadienyl proton resonances are shifted to higher field than those for hydroxyketone **2a**, and give rise to three sets of multiplets. A two proton multiplet at  $\delta$  4.28 ppm was assigned to  $\beta$ -protons on the hydroxy group side (reflecting the deshielding effect of the hydroxy groups), a four proton multiplet at  $\delta$  4.12 ppm from the  $\gamma$ -protons, and a two proton multiplet at  $\delta$  3.89 ppm assigned to the remaining  $\beta$ -protons (on the opposite side to the hydroxy groups).

The cyclohexane ring proton resonances of **5a** also give rise to three multiplets: a two proton multiplet at  $\delta$  2.13 (hydrogens 2'), a two proton multiplet at  $\delta$  1.26 (hydrogens 6'), and a six proton multiplet at  $\delta$  1.53 (hydrogens 3', 4' and 5'). A shift of the methyl group signal ( $\delta$  1.41 ppm) to a similar position as that in the spectrum of 1,1'-bis( $\alpha$ -hydroxyisopropyl)ferrocene [12] ( $\delta$  1.50 ppm), which may be used as a reference compound, points to axial locations of these groups relative to the cyclopentadienyl rings and to hydrogen bonding between the hydroxyl groups [7]. The diamagnetic deshielding effect of the cyclopentadienyl rings [8] can be seen even more clearly in the spectrum of **5c**, in which the methyl group resonances appear as two doublets at  $\delta$  0.68 and 0.82 ppm.

Replacement of the methyl by isopropyl groups causes only small changes in the relevant part of the spectrum. However, benzyl and phenyl groups have a significant influence on the <sup>1</sup>H NMR spectrum because of their strong diamagnetic anisotropy. Shifts of the cyclopentadienyl proton resonances to a higher field in the spectrum of **5f** indicates that the cyclopentadienyl ring is located within a shielding cone of the phenyl ring. Also shifted to higher field are the resonances of the phenyl *ortho* protons, which indicates that the phenyl rings are located above and below the cyclopentadienyls [8,9].

Larger changes in the spectrum were observed when phenyl substituents were present (**5g**). Because of strong downfield shift of the OH proton resonances, it can

be concluded that the OH groups lie close to the phenyl planes. The resonances of the bridge methylene proton signals are also shifted to lower fields. An upfield shift is observed, however, for the C(2') methylene protons, indicating that this methylene group lies in a shielding cone of the phenyl ring. The data suggest that there is no free rotation of the phenyl groups.

Because of the molecular symmetry, the  $^{13}\text{C}$  NMR spectra of diols **5** are simpler than those of analogous hydroxyketones **2**. Six resonances of the cyclohexane ring, and five resonances which could be assigned to the cyclopentadienyl ring, found in the  $^{13}\text{C}$  NMR spectra of **5**, support the conclusion drawn from the IR and  $^1\text{H}$  NMR spectra that the molecules of **5** are rigid with strong intramolecular hydrogen bonding. However, owing to the presence of a plane of symmetry (Fig. 1), the bridge methylene carbons C(2) and C(4) as well as the quaternary carbons C(1) and C(5) are equivalent, each giving one signal, at  $\delta$  50.3 and 72.0 ppm, respectively, in the case of the methyl derivative, **5a**. The first of the assignments was made on the basis of a comparison of the spectra of **5a** and **2a**, and of the absence of this peak in the spectrum of **13**, and was supported by the fact that the peak at  $\delta$  50.3 ppm was the methylene signal most affected by replacement of the methyl by an ethyl group, a  $\gamma$ -effect [10,11] (compare data for **5a** and **5b**). The second of these assignments was made on the basis of the off-resonance decoupled spectrum, which indicated the presence of quaternary carbon atoms, and also of comparison of the spectrum of **5a** with that of **2a**.

### Spectra and structures of ethers **7** and **9**

A structure similar to that of glycols **5** is expected for ethers **7** and **9**. The molecule is quite inflexible, however, and the bridge atoms occupy strictly defined positions in the space surrounding the ferrocene system. Dreiding models revealed that there is some strain in the molecule, which causes the cyclopentadienyl rings to be mutually inclined, as in molecules of [3]ferrocenophan-1-on [13] or [3]ferrocenophane-1,3-dione [14].

A characteristic feature of the  $^1\text{H}$  NMR spectra of these compounds is the resonance of the bridge terminal protons, which appears as a doublet of doublets in the region of  $\delta$  4.40–4.80. Two different coupling constant values for coupling of the proton on C(5) with C(4) protons confirm the rigidity of the bridge. Two independent resonances of the methyl groups arising from the isobutyl substituents in **7d**, at  $\delta$  0.70 and 0.93 ppm, provide additional evidence that the molecule is inflexible and that rotation of the group is somewhat restricted. The signals from the bridge methylene C(2) and C(4) protons have rather similar shifts, and this leads to a complex splitting pattern; detailed analysis of these signals is therefore difficult, and would require a special study.

Only one of ethers **7**, namely **7f**, was available in an amount sufficient for recording of the  $^{13}\text{C}$  NMR spectrum. A comparison of the  $^{13}\text{C}$  NMR spectrum of **7f** with that of **5f** (which bears the same substituent) reveals that in the case of the ether the cyclopentadienyl signals are shifted by about 2–3 ppm downfield. The bridge carbon signals of **7f** are shifted to higher field by a larger amount (5–8 ppm). These shifts cannot be simply explained in terms of substituent effects, and must arise from a difference in molecular geometry. The reported [12–15] ring-tilt for

[3]ferrocenophanes is 8–10°, and a similar value can be expected for molecules **7** and **9**.

## Experimental

Melting points are uncorrected. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a 100-MHz Tesla BS 567A spectrometer with CDCl<sub>3</sub> as solvent and tetramethylsilane as internal reference. IR spectra were recorded on a Specord 75 IR (Carl Zeiss, Jena) spectrophotometer for samples in hexachlorobutadiene mulls. Ether for Grignard reactions was dried by storage over potassium hydroxide pellets or molecular sieves (4A) for more than one week. Tetrahydrofuran (THF) and 1,4-dioxane were dried by refluxing the commercial solvents with sodium/benzophenone and distillation prior to use.

### *Grignard reagents*

All the Grignard reagents used, except for methylmagnesium chloride (purchased from Merck), were prepared before use from magnesium turnings and the appropriate alkyl or aryl halides. Their concentrations were established by adding an appropriate volume of the ethereal solution to water, evaporating the ether, and titrating the formed magnesium halogenohydroxide against 1 M hydrochloric acid.

*Reaction of spirodione 1 with methylmagnesium chloride.* To a stirred suspension of spirodione **1** (1.4 g, 4 mmol) in dry ether (50 ml) under nitrogen was added a solution of methylmagnesium chloride in THF (9 ml, 15.3 mmol). The stirring was continued at 20 °C for 24 h. The mixture was added to ice water (200 g), and additional ether (200 ml) was added. The ethereal layer was separated, washed with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue recrystallized from benzene/cyclohexane (30 + 10 ml). Pure 1-hydroxy-1-methyl-spiro[5]ferrocenophane-3,1'-cyclohexan-5-on (**2a**, 0.9 g) was obtained as orange-brown needles (Table 2). An additional portion of the product (0.1 g) was obtained by dilution of the filtrate with petroleum ether and storage of the solution at –5 °C.

*Reaction of the spirodione 1 with a large excess of ethylmagnesium iodide.* To a stirred suspension of the spirodione **1** (1.4 g, 4 mmol) in dry ether (60 ml) under nitrogen was added a solution of ethylmagnesium iodide (40 mmol) in ether (30 ml). The mixture was stirred for 24 h at room temperature and then added to ice-water (200 g). Ether (100 ml) was added and the ethereal layer was separated and dried over anhydrous magnesium sulfate, and the solvent was evaporated. The semi-solid product was triturated with n-hexane to give crude hydroxyketone **2b** (0.6 g). Recrystallization from n-hexane afforded an analytical sample of **2b** (Table 2).

*Reaction of the spirodione 1 with isobutylmagnesium iodide.* To a stirred suspension of spirodione **1** (2.1 g, 6 mmol) in dry ether (100 ml) under nitrogen was added a solution of isobutylmagnesium iodide in ether (17 ml, 18 mmol). The mixture was stirred for 24 h and then added to ice-water (200 g). Addition of further ether (100 ml), washing of the ethereal solution with water, drying over anhydrous magnesium sulfate, and evaporation of the solvent left a residue, which was subjected to column chromatography (silica gel, 100–200 mesh). The first fraction was eluted with benzene. TLC of that fraction indicated that it consisted of two compounds, and repeated chromatography with cyclohexane as an eluent gave ethers **7d** and **9**

(Tables 1 and 2). The second fraction was eluted with chloroform to give hydroxyketone **2d**. Elution with the same solvent gave a third fraction, from which starting spirodione **1** was recovered (330 mg, 16%). Finally, use of chloroform/ethyl acetate (10/1) as eluent gave a fourth fraction, which was judged to be hydroxyketone **3**.

*Reaction of spirodione 1 with a ten-fold excess of isobutylmagnesium iodide.* The reaction was carried out as described above but with spirodione **1** (1.75 g, 5 mmol) suspended in dry ether (80 ml) and isobutylmagnesium iodide (50 mmol) in ether (41.2 ml). Work-up was similar to that above. No unchanged spirodione **1** was found in this case.

*Other Grignard reactions of 1.* The procedures described above for Grignard reactions of **1** were used for the other related reactions and details of these are shown in Table 1.

*Reduction of spirodione 1 with sodium borohydride.* A stirred solution of spirodione **1** (0.70 g, 2 mmol) and sodium borohydride (0.40 g, 10 mmol) in ethanol (40 ml) was heated under reflux, and the progress of the reaction was monitored by TLC (silica gel, chloroform/ethyl acetate, 9/1). When reaction was complete (3 h), the mixture was added to cold water (200 ml) and extracted with chloroform (4 × 20 ml). The combined chloroform fractions were dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure, and the residue was recrystallized from cyclohexane/benzene (10/1). The first crop of crystals of 1-hydroxyspiro[5]ferrocenophane-3,1'-cyclohexan-5-one (**3**) (0.40 g). Dilution of the filtrate with n-hexane and freezing afforded a second crop of **3** (0.21 g). The total yield of **3** was 87%.

*Reaction of hydroxyketone 2b with ethylmagnesium iodide.* To a solution of ethylmagnesium iodide prepared from magnesium turnings (0.24 g, 10 mmol) (activated with iodine (0.25 g, 1 mmol)) and ethyl iodide (0.64 ml, 8 mmol) in ether (10 ml) was added **2b** (0.25 g, 0.66 mmol). The mixture was stirred overnight under argon and water (0.5 ml) then was added. The mixture was set aside at room temperature in a beaker to allow the ether to evaporate off. The residue was triturated with THF (10 ml) and the solution filtered, then diluted with water (2 ml) and stored at -5 °C for 20 h. The orange needles which precipitated were filtered off, washed with ether/hexanes (5 + 5 ml), and dried in a vacuum oven at 40 °C. The product (0.19 g) was analytically pure 1,5-diethyl-1,5-dihydroxyspiro[5]ferrocenophane-3,1'-cyclohexane (**5b**) (Table 2).

*Preparation of deuterium labelled hydroxyketone 10.* To a solution of deuterium oxide (1.5 ml, 83 mmol) in dry dioxane (50 ml) was added liquid potassium/sodium alloy (0.5 ml, 13 mmol). Evolution of gaseous dideuterium was observed. The mixture was stirred under argon overnight, after which the metal had disappeared. Compound **2a** (0.38 g, 1.04 mmol) was added and the mixture was stirred under reflux for 7 h, then added to ice/water (150 g) and neutralized with acetic acid. The precipitate was filtered off, washed with water, dried in a vacuum oven, and shown to be **10** (0.35 g). According to the <sup>1</sup>H NMR spectrum, one of the C(4) methylene protons of **2b** has been replaced by deuterium to the extent of ca. 90%, and the second to the extent of ca. 40%.

*Preparation of deuterium labelled dione 11.* Freshly distilled diglyme (75 ml) and deuterium oxide (2 ml) were placed in a 250 ml vial. The air in the vial was replaced by argon and liquid potassium/sodium alloy (0.5 ml, 13 mmol) was added. After the metal had completely reacted, spiroferrocenophanedione (**1**, 1.5 g) was added.

The vial was sealed under reduced pressure and kept in an oil bath at 160–180 °C for 6 h, then cooled and opened. The mixture was poured into ice-water (200 g), neutralized with acetic acid, and diluted with methanol (100 ml). The precipitate was filtered off, washed with methanol, and chromatographed on basic aluminum oxide with chloroform as eluent. The sample of **11** (0.66 g) obtained contained, according to its <sup>1</sup>H NMR spectrum 43% of deuterium incorporated into the methylene groups of C(2) and C(5).

*Reaction of deuterium labelled dione 11 with methylmagnesium iodide (molar ratio 1/3).* To a solution of methylmagnesium iodide prepared from magnesium turnings (0.12 g, 5 mmol) and iodomethane (0.31 ml, 5 mmol) in dry ether (20 ml) was added **11** (0.65 g, 1.9 mmol). The mixture was stirred overnight at room temperature, added to water, neutralized with acetic acid, and extracted with chloroform. The chloroform solution was washed with water, and dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue mixture was subjected to column chromatography in silica gel with benzene/chloroform/ethyl acetate (6/3/1) as an eluent to give hydroxyketone **12** (0.06 g) and unchanged dione **11** (0.25 g).

*Reaction of deuterium labelled dione 11 with a large excess of methylmagnesium iodide.* To a solution of methylmagnesium iodide prepared from iodomethane (1.87 ml, 30 mmol) and magnesium turnings (0.07 g, 40 mmol) in ether (30 ml) was added a solution of dione **11** (0.10 g, 0.28 mmol) in dry THF (5 ml). The mixture was stirred at 20 °C for 4 h and then added to water (50 ml). The organic substances were extracted into dichloromethane (50 ml), and the extract was dried over anhydrous potassium carbonate. Evaporation of the solvent left pure dideuteriodiol **13** (0.08 g).

## Acknowledgment

Support of this work by the Polish Academy of Sciences (Grant No. CPBP 1.13.3.23) is gratefully acknowledged.

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