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FERROCENES AS HAEMATINICS

BY

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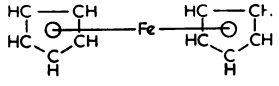
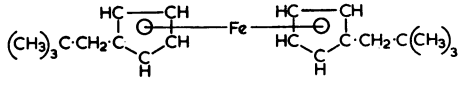
Ferrocene is the name given to biscyclopentadienyl iron, $Fe(C_5H_5)_2$, because it behaves like benzene in many chemical reactions (Woodward, Rosenblum & Whiting, 1952). Ferrocene was discovered in 1951 by Kealy & Pauson (1951) and independently by Miller, Tebboth & Tremaine (1952). Since then many derivatives of ferrocene have been prepared. The advances made in the chemistry of this new type of organometallic compound have been reviewed many times (for instance, Fisher & Fritz, 1959; Wilkinson & Cotton, 1959; Raush, 1963). There are still some doubts as to the exact nature of the bond between the divalent iron atom and the two cyclopentadienyl ligands.



Ferrocene



Dineopentyl ferrocene

Ferrocenes were examined as haematinics in rats because they are iron-containing compounds in which the metal cannot become ionic without breaking up the very stable aromatic structure of which it is an integral part. It was hoped that in animals the ferrocenes would behave in the same way as other simple aromatic compounds, some of which are well absorbed when given by mouth and then metabolized. A number of ferrocenes were found to be well absorbed and then metabolized leaving their iron available to be incorporated into haemoglobin. Some of the procedures used to prepare the ferrocenes used in these experiments have already been described (Leigh, 1964).

METHODS

The experimental methods used were chosen taking into consideration that the iron in ferrocenes is not ionizable without previous destruction of the molecule, that much more iron is absorbed from ferrocenes than from other iron compounds and that many of the ferrocenes are insoluble in water but soluble in fats and organic solvents.

Dosage

It was found convenient, and considered more relevant, to express the doses as mg of iron per kg instead of the more usual mg of compound per kg. The compounds tested had between 5 and 30% iron. Water-insoluble compounds were dosed routinely as fine dispersions in 1.5% aqueous "Dispersol O.G." (trade mark of Imperial Chemical Industries Ltd.), and occasionally as solutions in various oils. The standard dose to determine absorption and cure of anaemia was 100 mg/kg of iron. This dose contains about twice the average normal iron content of the body of mammalians. Suspensions and solutions were dosed by stomach tube in a volume not exceeding 2 ml. for rats and 0.5 ml. for mice.

Measurement of absorption

The iron contents of the excreta of treated and untreated groups of five rats were compared. The animals were kept for 1 hr each day in a cage in which pelleted food was freely available. The excreta passed during this time were ignored. For the remainder of the time the animals were kept in metabolism cages without food but with water available at all times. As judged by the amount of food consumed, the rats became used to this form of life in 2 or 3 days. Then for 2 days the faeces and urine were collected and their total content of iron estimated by wet ashing. The normal iron output was about 1 mg/rat/day in the faeces and less than one-hundredth of this in the urine. The rats were then dosed and the iron content of their faeces and urine estimated until the daily output of the dosed and the control group was the same. Four to five days was required for this (see Table 4).

Treatment of anaemia

The rats used were kept in galvanized cages with open mesh bottoms to minimize coprophagy. Their only food was pasteurized milk which is practically free from iron (Davidson, Meiklejohn & Passmore, 1959). The rats were bled by cardiac puncture (Eamonson, 1961) three or four times at intervals of 4 or 5 days, 3 to 4 ml. of blood being removed each time. The haemoglobin concentration of the rats' blood after this procedure was about half that of normal animals. It did not increase in the course of 2 months, showing that the iron reserves of their livers had been mobilized and that no iron was being absorbed by the animals. On injection of an iron-dextran complex (Imferon; Benger Laboratories Ltd.), daily oral doses of ferrous sulphate or a diet of rat cubes, the haemoglobin increased rapidly, showing that only lack of iron prevented the animals from making haemoglobin. Usually estimations of haemoglobin were made 3 days and 1, 2 and 3 weeks after a single oral dose of the ferrocene examined. Animals treated with an injection of Imferon in the muscles of the thigh were used as positive controls and rats dosed with the dispersing agent as negative controls.

Iron estimations

Iron was determined colorimetrically using thiocyanate as a reagent. The samples were heated with a suitable amount of a mixture of five parts by volume of concentrated sulphuric acid and two parts of 60% perchloric acid until all the organic matter had disappeared. The digest was made up to a suitable volume with water. A 10-ml. sample was mixed with 5 ml. of 20% potassium thiocyanate and extracted with 10 ml. of glass-distilled amyl alcohol. The absorption of light at 500 mμ by the amyl alcohol layer was determined in a previously calibrated colorimeter. Benzene- and chloroform-soluble iron was determined by shaking the biological fluid or the homogenized tissue at least twice with five volumes of the solvent. The solvent layers were separated, by centrifuging if necessary, filtered through paper to remove traces of water, an aliquot was evaporated, and iron was estimated by wet ashing of the residue as previously described.

Haemoglobin estimations

Blood from the tails of the rats was collected over solid sodium citrate. To 4 ml. of 0.4% ammonia 0.02 ml. of citrated blood was added and the absorption of light at 540 mμ was measured in a previously calibrated colorimeter. The results were expressed as percentages of normal, assuming 14 g of haemoglobin per 100 ml. of blood as normal.

RESULTS

Ferrocene

A single oral dose corresponding to 100 mg/kg of iron, about 0.5 LD50, produced in anaemic rats an increase in haemoglobin somewhat smaller than that following an injection of Imferon containing the same amount of iron (Table 1).

Repeated daily doses of ferrocene (10 mg/kg of iron) given by mouth to mice resulted in the accumulation of substantial amounts of iron in their livers (Table 2).

Single oral doses of ferrocene corresponding to 150 mg/kg of iron failed to kill mice, but all of a group of five died after a dose corresponding to 250 mg/kg. Two out of ten mice

TABLE 1

TREATMENT OF ANAEMIA OF RATS WITH FERROCENE

Single doses corresponding to 100 mg/kg of iron were given; ferrocene by mouth as aqueous dispersion, Imferon by injection in the thigh. Means for three rats. Times refer to days after dosing

	Haemoglobin (% of normal) on day				
Treatment	0	7	13	21	28
Ferrocene	50	64	66	82	84
Imferon	57	72	78	90	98
Control	56	58	56	58	60

TABLE 2

INCREASE OF IRON IN THE LIVER OF MICE

Mean liver iron in five mice receiving by mouth repeated daily doses of ferrocene corresponding to 10 mg/kg of iron. The mice were killed 1 week after the last dose

	Liver iron (mg) after No. of doses				
Treatment	1	5	10	15	20
Ferrocene	0·10	0·13	0·36	0·53	0·84
Control	0·10	0·10	0·10	0·12	0·11

were killed by a daily dose of ferrocene corresponding to 12.5 mg/kg of iron repeated fifteen times, but half this dose could be repeated twenty-eight times without causing fatalities. Ferrocene was more toxic when given as an aqueous suspension by intraperitoneal injection; a single dose corresponding to 100 mg/kg of iron killed seven out of ten mice. Injection in the thigh of the same dose cured anaemic rats as rapidly as when given by mouth and was not lethal.

Ferrocene was absorbed almost quantitatively by rats from an oral dose corresponding to 100 mg/kg of iron. Between one-fifth and one-tenth of the iron absorbed was eliminated in the urine. This excreted iron was not ionic because the untreated urine failed to give a reaction with thiocyanate, or ferri- or ferrocyanate. The iron was probably in the form of a water-soluble ferrocene. On oxidation with persulphate the urine became green, presumably because the water-soluble ferrocene was transformed into the corresponding blue ferricinium. Excess of oxidizing agent liberated the iron in an ionic form which reacted with thiocyanate and ferrocyanide. The water-soluble metabolite was not extractable with organic solvents, except in very small amounts by butyl or amyl alcohol.

Dineopentyl and other substituted ferrocenes

Ferrocene mono- and dicarboxylic acids, and mono- and disulphonic acids were as, or more, toxic than the parent compound, and they were also excreted in the urine. Of a series of acyl, alkyl and phenyl ferrocenes tested, those shown in Table 3 combined low toxicity with good absorption and were effective in curing anaemia in bled rats. None of them was excreted in the urine. The lower homologues examined (one to three carbon atoms in the substituents, mono- and disubstituted) were as, or more, toxic than the unsubstituted ferrocene and partially excreted in the urine. Higher homologues (seven or more carbon atoms) were not well absorbed. The acyl derivatives were more toxic than the corresponding alkyl ferrocenes. Disubstituted ferrocenes were less toxic and less well absorbed than the monosubstituted compounds. The monophenyl ferrocenes tested were not particularly well absorbed, except the *p*-aminophenyl which was toxic and the *p*-hydroxy and *p*-carboxyphenyl ferrocenes which were excreted almost quantitatively in the urine.

TABLE 3

TOXICITY, ABSORPTION AND REGENERATION OF HAEMOGLOBIN BY FERROCENES GIVEN BY MOUTH

Toxicity refers to the number of doses of aqueous dispersions which killed five of ten mice. Absorption gives means of groups of five rats. Haemoglobin regeneration gives the content as the percentage of normal (14 g/100 ml.), before and 3 weeks after dosing

	Toxicity in mice (doses) for mg/kg of iron			Absorption (%) in rats for mg/kg of iron	Regeneration of haemoglobin (%) in rats for mg/kg of iron × No. of daily doses						
Preparation	1,000	500	250	100	100×1	50×1	25×1	10×1	10×5	10×15	5×15
Ferrous sulphate	1	1	1-3	—	—	63–63	—	—	67–80	56–89	58–80
Imferon (parenteral)	1-2	—	—	—	—	65–100	60–95	75–83	—	64–92	—
Name of ferrocene and structure of substituents:											
Dineopentyl ferrocene [$-CH_2.C(CH_3)_3$]	>50	>50	>50	50–60	63–97	62–87	57–74	60–66	65–90	—	60–88
Di-*t*-butyl ferrocene [$-C(CH_3)_3$]	2	2	4	71	60-95	50–80	58–76	63–58	60–95	—	—
Di-*t*-pentyl ferrocene [$-C(CH_3)_2.CH_2.CH_3$]	5	5	>16	41	57–90	62–82	58–67	60–85	—	—	—
Monobenzyl ferrocene [$-CH_2.C_6H_5$]	2	2	3	80	57–95	53–83	55–73	—	67–97	—	—
Monophenylethyl ferrocene [$-CH_2.CH_2.C_6H_5$]	2	2	5	66	65–93	48–73	65–74	—	—	—	—

Dineopentyl ferrocene was chosen as an example of a relatively nontoxic and well-absorbed ferrocene for examination of the fate of its iron. Dineopentyl ferrocene contains 17.2% of iron. The doses expressed as mg/kg are about six times the dose expressed as mg/kg of iron. Between 50 and 55% of the iron given by stomach tube as an aqueous suspension, at a dose corresponding to 100 mg/kg of iron, was absorbed by rats kept on a normal laboratory diet which was stated to contain 3% oil. Similar results were obtained with guinea-pigs, dogs and rhesus monkeys. The yellow ferrocenes could be detected in the stomach and the upper part of the gut, above the end of the bile duct. There was no ferrocene in the bile of guinea-pigs which had been dosed with dineopentyl ferrocene.

Absorption was increased to 60 to 70% when the ferrocene was given dissolved in more than 1 ml. of corn oil per rat. Absorption of 50 to 55% was obtained from aqueous dispersions when the rats were fed the normal laboratory diet extracted with petroleum ether and therefore presumably free of fat. With higher doses of aqueous dispersions the relative absorption was less, 30 to 35% from a dose corresponding to 500 mg/kg of iron (or over 3 g/kg of compound) and 20 to 25% from a dose corresponding to 1 g/kg of iron (or over 6 g/kg of compound).

Table 4 shows that most of the nonabsorbed iron was eliminated in the faeces during the first 3 days after dosing rats with aqueous dispersions of dineopentyl ferrocene. A similar picture was obtained with guinea-pigs, dogs and monkeys. Three or more daily doses of dineopentyl ferrocene, corresponding to at least 100 mg/kg of iron resulted in the fat of the animals becoming yellow. About a week after the last dose the discoloration disappeared. Dineopentyl and other ferrocenes are yellow compounds soluble in fat. The fat of mice which received a single dose of dineopentyl ferrocene corresponding to 1 g/kg of iron was discoloured. The benzene-extractable iron of the homogenized carcass of the

TABLE 4

FATE OF THE IRON OF DINEOPENTYL FERROCENE IN RATS

The compound was given as an aqueous dispersion to 200-g rats at a dose corresponding to 100 mg/kg of iron. Values are means for five rats, and refer to iron contents

Days after dosing	Iron (% of dose) in		Iron in				
			Liver			Brain	Blood
	Faeces	Stomach	Organ weight (g)	Total (mg)	Chloroform-soluble (mg)	Total (mg)	Chloroform-soluble (μg/ml.)
Before	0·0	0	23	4·6	0·00	0·037	0·0
0·12	—	90	20	5·0	0·16	—	0·2
0·25	—	75	22	5·3	0·16	0·038	0·0
1	17·5	13	24	7·1	0·30	0·053	0·4
2	31·0	0	29	9·3	0·90	0·092	0·5
3	17·6	0	38	10·1	0·40	0·059	0·4
4	7·8	—	—	—	—	0·052	—
5	0·0	—	33	10·0	0·00	0·042	0·2

animals increased reaching a maximum of 2.3 mg of iron per 20 g of mouse the day after dosing and then decreased. Estimation of the total iron in the mice showed that, like rats, they absorbed and retained over half the iron contained in a dose corresponding to 100 mg/kg of iron. As shown in Table 4, the iron content of the liver behaved in a similar way; the amount extractable with chloroform increased in the first 2 days and then decreased.

The size of the livers also increased as a result of the treatment with dineopentyl ferrocene. At 1 week after treatment with a single oral dose corresponding to 100 mg/kg of iron, the average weight of the liver of treated animals was about one-third greater than that of the controls (twenty-five rats in each group). An increase from an average of 0.3 to 9.0 mg/kg of iron was observed in a group of ten rats which received forty daily oral doses of dineopentyl ferrocene each corresponding to 100 mg/kg of iron. No significant histological abnormalities could be found in the liver, other than deposition of large amounts of iron. The treated animals grew at the same rate as an untreated control group.

Effect of fat on the toxicity of ferrocenes

The toxicity of some ferrocenes to mice increased when they were given by mouth as solutions in oils (cod liver, olive, arachis or corn oil) but not in medicinal paraffin. Single doses corresponding to 1 g/kg of dineopentyl, di-*t*-butyl, di-*t*-pentyl, monobenzyl or monophenylethyl ferrocenes did not kill mice when given by mouth as aqueous dispersions (formulae in Table 3, which also shows the lethality of repeated daily doses). Except with di-*t*-butyl ferrocene doses of this size killed some of the animals when the ferrocenes were dissolved in 1 ml. of oil per mouse. The toxicity of dineopentyl, and probably of other ferrocenes also, depends both on the amount of fat and of ferrocene given. Ten consecutive daily doses of dineopentyl ferrocene corresponding to 100 mg/kg of iron were not fatal to mice when the solvent was cod liver oil (0.25 ml./mouse), but when it was given in 1 ml./mouse only one out of five survived. With a dose corresponding to 250 mg/kg of iron, three of five mice died after eight doses each dissolved in 0.25 ml./mouse and three of five died after five such doses dissolved in cod liver oil 1.0 ml./mouse. Rats kept on a normal diet (3% fat) survived without loss of weight after thirteen daily doses of an aqueous dispersion of dineopentyl

ferrocene corresponding to 500 mg/kg of iron, but this treatment killed three out of five when the diet consisted exclusively of peanuts which had 48% fat. The survivors lost a considerable amount of weight; control groups gained the same weight with either diet.

Convulsant and " proconvulsant " actions of ferrocenes

Coarse tremors and sometimes convulsions were seen in toxicity experiments in mice, especially after repeated sublethal daily doses. Convulsions invariably followed oral doses of dimethylaminoethyl ferrocene corresponding to 25 mg/kg of iron or more. Rats treated with solutions of dineopentyl ferrocene in oil sometimes had violent convulsions, not necessarily fatal, which were often initiated by disturbing the animals, either by handling them or by opening the cages. The convulsions were so severe that they often resulted in dislocation of their spines. The milder forms of convulsions resembled those produced by electroshock. Dineopentyl ferrocene decreased the time of about 5 sec required for an electric current passed across the ears of rats to produce maximal convulsions (Table 5). Anticonvulsants are known to increase this time (method of Bogue & Carrington, 1953). The " proconvulsant " action of ferrocenes, like their toxicity, was increased by fats but not by medicinal paraffin. The increased sensitivity to electroshock was not appreciably increased in the first 8 hr after dosing, was maximal the next day and then decreased at a rate which depended on the dose (Table 5). Similar results to those for dineopentyl ferrocene were obtained with unsubstituted ferrocene, di-*t*-butyl, di-*t*-pentyl and monophenylethyl ferrocenes.

TABLE 5

" PROCONVULSANT " ACTION OF DINEOPENTYL FERROCENE

Values are mean percentage decreases for groups of ten rats (100 g) of the time required to produce maximal convulsions by a current of 6·5 mA, 20 to 30 V and 50 cycles/sec applied across the ears of the animals

Dose of		Decrease in time (%) in days after dosing			
Oil (ml./rat)	Iron (mg/kg)	1	2	3	4
0	50	23	15	−1	—
0·25	50	23	15	−6	—
0·5	50	50	26	−4	—
1·0	0	−4	−17	−21	—
1·0	12·5	10	−16	11	—
1·0	25	26	10	1	—
1·0	50	36	27	14	−3
1·0	100	42	36	23	−9
1·0	200	57	50	42	21

DISCUSSION

The rejection mechanisms present in the intestine which regulate the absorption of iron are apparently arranged to deal only with ions of this metal. They fail to operate when presented with compounds containing the ferrocene nucleus, from which the iron cannot be ionized without disrupting the very stable molecule. The physical and chemical properties of ferrocenes are more akin to those of aromatic hydrocarbons, such as benzene and naphthalene, than to those of salts of iron, however chelated these salts may be. This is reflected in the behaviour of the ferrocenes in the animal body. Like the lower homologues of benzene, the ferrocenes with small aliphatic substituents are well absorbed when given by mouth. The higher homologues of ferrocene, like those of benzene, fail to be absorbed. Once ferrocenes are in the body they continue to behave as benzenoid compounds. Like

benzoic acid and benzene sulphonic acids, the sulphonated ferrocenes and the ferrocene carboxylic acids are eliminated in the urine, presumably undegraded, though perhaps conjugated. The mechanisms present in the kidney which normally prevent iron passing into the urine do not recognize the metal as such when it is presented to them as a ferrocene derivative.

The presence of iron in the urine as water-soluble ferrocenes, after oral administration of water-insoluble unsubstituted ferrocene, or some of its lower homologues, is perhaps evidence that the ferrocene nucleus, like that of aromatic hydrocarbons, can be transformed in the body into water-soluble compounds without losing its identity. Not all the absorbed ferrocenes are eliminated in the urine; with most of them the whole of the absorbed iron remains in the body. The fate of the absorbed iron has been examined in some detail in ferrocene itself, and in some of the less-toxic and well-absorbed ferrocarbons, especially in dineopentyl ferrocene. In mice and rats the yellow ferrocenes could be seen in the stomach and duodenum during the first few hours after ingestion. The intestine was stained yellow until just below the point at which it is joined by the bile duct. This may indicate that, like many other water-insoluble substances, the ferrocenes are absorbed with the help of the bile acids. There was no ferrocene present in the bile of guinea-pigs which had been dosed with dineopentyl ferrocene.

The results obtained with dineopentyl and other ferrocenes indicate that these compounds when given by mouth are absorbed in the intestine, pass into the blood, can be retained by the fats of the animals and are eventually metabolized, the iron being then stored in the liver in a form suitable for haemoglobin synthesis. The presence in the blood of iron soluble in organic solvents shows that it contains ferrocenes. The retention by fats is shown by their yellow discoloration and by the presence of benzene-soluble iron in the carcass. All the iron present in the liver eventually becomes insoluble in benzene, indicating that the ferrocenes have been metabolized. The haemoglobin of rats made anaemic by bleeding is restored to normal after oral treatment with dineopentyl and other ferrocenes, indicating that the absorbed iron becomes available for the synthesis of the pigment.

The toxicity of ferrocenes is of a different type from that due to salts of iron, and it is thought to be due to the ferrocene nucleus and not to the iron they contain. Animals receiving lethal doses of water-soluble ferrocenes died in convulsions so soon after dosing that it is unlikely that the ferrocene had a chance of being metabolized. Water-insoluble ferrocenes acted more slowly, but the symptoms were similar, coarse tremors and convulsions preceding death. It is possible that the insoluble ferrocenes were metabolized to toxic water-soluble compounds still containing the intact ferrocene nucleus. Presumably these toxic compounds were formed fast enough from ferrocene itself, and from the toxic lower homologues, to escape further degradation and appear in the urine. Perhaps the higher homologues were less toxic because, having greater affinity for fats, they were metabolized more slowly and the hypothetical toxic water-soluble materials were degraded further as soon as they were formed.

The increased sensitivity to electroshock by the water-insoluble dineopentyl ferrocene and similar water-insoluble ferrocarbons is likely to be due to the same process which produces convulsions. No convulsions were seen until the day after dosing, nor was the sensitivity to electroshock increased before then. Both actions are potentiated by fats. The mechanism by which the fats increase the toxicity of ferrocenes has not been elucidated.

The fats increase somewhat the amount of ferrocene absorbed. This does not explain the increased toxicity, since a similar increased absorption can be obtained with impunity by giving more ferrocene in the absence of an excess of fat. If fats increase the formation of the hypothetical toxic water-soluble metabolites they do so in such a way that these metabolites do not appear in the urine when dineopentyl ferrocene is dosed.

SUMMARY

1. The behaviour of ferrocenes in rats or mice has been examined because the iron of these organometallic compounds cannot become ionized without destruction of the stable aromatic system of which it forms an integral part.

2. Rats made iron-deficient by bleeding were used to measure the availability of iron for the production of haemoglobin. In control rats the iron absorbed was measured by estimation of the metal in the faeces. Mice were used to determine lethality.

3. Some ferrocenes are well absorbed from the gastrointestinal tract. Some of the absorbed ferrocenes are eliminated in the urine. The mechanisms which regulate the metabolism of iron appear unable to recognize the metal as such when it is presented to them in the form of ferrocenes.

4. The ferrocenes which are absorbed and retained in the body are metabolized, liberating their iron in a form which can be used for making haemoglobin. Some ferrocenes, such as dineopentyl ferrocene, are sufficiently nontoxic to be able to cure, in a single oral dose, the anaemia of rats whose haemoglobin had been reduced to half the normal level by bleeding.

5. The toxicity of the very innocuous ferrocarbons examined was increased when large amounts of fat were given at the same time. Convulsions were a symptom of their toxicity. The sensitivity of rats to electroshock convulsions was increased the day after giving these ferrocenes by mouth. This effect was greater when fat was given at the same time.

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