

## ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM EXPERIMENTAL STATION, EXPLOSIVES DEPARTMENT, E. I. DU PONT DE NEMOURS &amp; CO., WILMINGTON 98, DEL.]

Reaction of Iron Pentacarbonyl with *gem*-Dihalides

BY C. EUGENE COFFEY

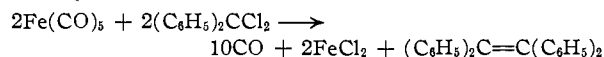
RECEIVED OCTOBER 28, 1960

Iron pentacarbonyl underwent a facile reaction with compounds of the type  $R_2CX_2$ , where R is phenyl, cyano, carbalkoxy or halogen, and X is chlorine or bromine. With  $R = p\text{-R}'C_6H_4$  (where R' is hydrogen, methyl, *t*-butyl, methoxy, chloro or nitro) the reaction gave tetrasubstituted tetraphenylethylenes,  $(p\text{-R}'C_6H_4)C=C(p\text{-R}'C_6H_4)$ . With other R groups the reaction products were more complex. Nickel tetracarbonyl, mercury iron tetracarbonyl, bis-( $\pi$ -cyclopentadienyliron(I)-dicarbonyl) and dipyridinetungsten tetracarbonyl, but not tungsten hexacarbonyl or chromium hexacarbonyl, reacted with dichlorodiphenylmethane to produce tetraphenylethylene.

It is a well-established fact that certain metal carbonyls react with halogenated organic compounds. Criegee<sup>1</sup> recently took advantage of this reactivity to prepare a nickel chloride complex of tetramethylcyclobutadiene from nickel tetracarbonyl and 3,4-dichlorotetramethylcyclobutene. Wilkinson<sup>2</sup> carried out a clean-cut oxidation of  $\pi$ -cyclopentadienylmolybdenum tricarbonyl hydride to  $\pi$ -cyclopentadienylmolybdenum tricarbonyl chloride with carbon tetrachloride as the oxidizing agent. Webb<sup>3</sup> produced coupling of allyl radicals by treating allyl halides with nickel carbonyl.

## Results

This paper reports a new reaction of iron pentacarbonyl (and certain other metal carbonyls) with *gem*-dihalides. This carbonyl reacted vigorously with dichlorodiphenylmethane in inert solvents with evolution of five moles of carbon monoxide, precipitation of ferrous chloride and formation of tetraphenylethylene in good yield in accord with the equation



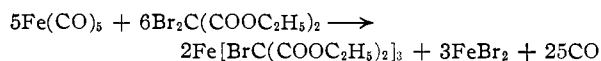
The reaction mixture passed through several highly colored stages, indicative of intermediate complexes, but the only product that could be isolated was the ethylene.

A similar reaction was observed with *p,p'*-disubstituted dichloro-(or dibromo)-diphenylmethanes. Thus, bis-(*p*-chlorophenyl)-dichloromethane, bis-(*p*-nitrophenyl)-dibromomethane, bis-(*p*-tolyl)-dichloromethane, bis-(*p-tert*-butylphenyl)-dichloromethane and bis-(*p*-methoxyphenyl)-dichloromethane all gave the corresponding tetrasubstituted tetraphenylethylene. The nitro and *t*-butyl substituted ethylenes were previously unreported. In benzene solution, 9,9-dibromofluorene gave bisfluorenylidene, but in dioxane the product was a mixture of bisfluorenylidene and 9,9'-dibromobisfluorenyl.

The reaction appears to be general for *p*-substituted dichloro (or dibromo) diphenylmethanes. Although only *p*-substituted compounds were used, owing to their ready availability, there is no reason why *o*- and *m*-substituted compounds should

not give similar results. Iron pentacarbonyl is an inexpensive, commercially available compound and the *gem*-dihalides are usually easy to prepare from benzophenones with phosphorus pentachloride or by bromination of diphenylmethanes. Therefore the reaction provides a convenient laboratory synthesis for substituted tetraphenylethylenes.

Iron pentacarbonyl also reacted with diethyl dibromomalonate to give a near quantitative yield of an interesting product completely different from the expected tetraethyl ethylenetetracarboxylate. The product was a deep purple, hydrocarbon-soluble, crystalline solid which was rapidly decomposed by alcohol or damp air with the formation of ethyl monobromomalonate. Chemical analysis and the infrared spectrum of the compound strongly support its formulation as tris-(diethyl bromomalonato)-iron(III),  $Fe[BrC(COOEt)_2]_3$ , analogous to tris-(2,4-pentanediono)-iron(III).<sup>4</sup> The reaction must be



The infrared spectrum of the compound showed only very weak absorption at  $1755\text{ cm}^{-1}$ , where diethyl dibromomalonate exhibits a strong carbonyl stretching band, but an intense new band appeared at  $1590\text{ cm}^{-1}$  which was assigned to a C-O stretch with a bond order of 1.5. This is entirely consistent with the interpretation<sup>5</sup> of the spectrum of tris-(2,4-pentanediono)-iron(III).

Dibromomalononitrile reacted vigorously with iron pentacarbonyl in inert solvents even at  $-80^\circ$ . However, a very complicated mixture of products ensued (fourteen colored bands were detected in one attempt to separate the products by chromatography on alumina). Carrying out the reaction in ethanol resulted in the formation of low yields of a compound which was identified as the ferrous salt of ethyl dicyanoacetate,<sup>6</sup>  $Fe[OC(OC_2H_5)=C(CN)_2]_2$ . A similar compound,  $Fe[OC(OCH_3)=C(CN)_2]_2$ , was formed when the reaction was carried out in methanol.

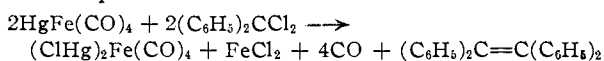
Iron pentacarbonyl also reacted with carbon tetrachloride (a known reaction<sup>7</sup> which produces

(1) R. Criegee and G. Schroder, *Ann.*, **623**, 1 (1959).  
 (2) T. S. Piper and G. Wilkinson, *Naturwissenschaften*, **42**, 625 (1955).  
 (3) I. D. Webb and G. T. Borchardt, *J. Am. Chem. Soc.*, **73**, 2654 (1951).

(4) G. T. Morgan and H. W. Moss, *J. Chem. Soc.*, **105**, 189 (1914).  
 (5) Cl. Duval, R. Freymann and J. Lecomte, *Bull. soc. chim. France*, 106 (1952).  
 (6) W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.*, **80**, 2788 (1958).  
 (7) A. Mittasch, *Z. angew. Chem.*, **41**, 827 (1928).

mostly tar and some hexachloroethane). Similar reactions occur with carbon tetrabromide, benzotrichloride and ethyl dibromoacetate. However, no reaction occurred with chloroform, *t*-butyl bromide, 2,2-dibromopropane, methylene chloride, methylene iodide,  $\alpha$ -chlorotoluene,  $\alpha,\alpha$ -dichlorotoluene, triphenylmethyl chloride, 1,2-dibromo-1,2-diphenylethane or allyl chloride.

Other metal carbonyls also reacted with *gem*-dihalides. Dichlorodiphenylmethane was used to determine the scope of this reaction. Chromium and tungsten hexacarbonyl did not react in refluxing benzene, presumably because of the effective shielding of the metal atom by the carbonyl ligands. A substituted group VI carbonyl, di-pyridinetungsten tetracarbonyl, did react to give tetraphenylethylene as did nickel tetracarbonyl, bis-( $\pi$ -cyclopentadienyliron(I)dicarbonyl) and mercury iron tetracarbonyl. The reaction with mercury iron tetracarbonyl proceeded according to the equation



### Discussion

Iron pentacarbonyl reacts with organic halides (at reflux in benzene) if two conditions are met. First, the halide must be activated by at least one, and preferably two, groups such as cyano, carbalkoxy, phenyl or halogen (in decreasing order of effectiveness). Second, there must be at least two halogens on the same carbon atom or in very close proximity to each other. In all cases but one the halogens were on the same carbon atom, but 1,2-dichloro-1,1,2,2-tetraphenylethane also reacted, forming tetraphenylethylene. Molecular models of this halide reveal that the halogens (in the rotamer with the closest approach of halogens) are as close as in a *gem*-dihalide and it is perhaps not surprising that reaction occurred. In no case did reaction occur with mono-halogenated compounds, even when the halide was as strongly activated as that in triphenylmethyl chloride.

The second condition suggests that the reaction with *gem*-dihalides involves a carbene intermediate. However, treating dichlorodiphenylmethane with iron pentacarbonyl in the presence of cyclohexene did not produce the expected carbene-cyclohexene addition product 7,7-diphenylnorcaradiene. The reaction also was carried out with methyl methacrylate as a solvent, but the only product was tetraphenylethylene; neither 1-methyl-1-carbomethoxycyclopropane (indicative of a carbene intermediate) nor polymethyl methacrylate (which would indicate a free radical intermediate) was formed. One indication of a carbene intermediate was obtained by conducting the same reaction in benzene in the presence of a large excess of sulfur. Thiobenzophenone, the addition product of  $(\text{C}_6\text{H}_5)_2\text{C}=\text{C}:$  with S, was isolated from the reaction mixture. However, the significance of this result is uncertain since mechanisms other than one involving a carbene intermediate could lead to the same product.

**Acknowledgments.**—I am grateful to Dr. H. M. Hubbard for reviewing the manuscript and for

many helpful suggestions. I am also indebted to several of my colleagues at this Laboratory for advice on problems on organic synthesis.

### Experimental

Mercury iron tetracarbonyl,<sup>8</sup> [ $\pi$ - $\text{C}_5\text{H}_5\text{Fe}(\text{CO})_2$ ]<sub>2</sub>,<sup>9</sup> ( $\pi$ -mesitylene)Cr(CO)<sub>3</sub><sup>10</sup> and W(CO)<sub>4</sub>(pyridine)<sub>2</sub><sup>11</sup> were prepared by literature methods.

**Bis-(*p*-nitrophenyl)-dibromomethane.**—Refluxing 25 g. (0.10 mole) of bis-(*p*-nitrophenyl)-methane and 12.2 ml. (0.22 mole) of bromine in 200 ml. of carbon tetrachloride for 6 hr. under irradiation by an ultraviolet lamp and subsequent vaporizing of the solvent gave a yellow crystalline product. Recrystallization from benzene-hexane and from methylene chloride-petroleum ether gave 20 g. (64%) of product, m.p. 164–166°. Chemical analysis indicated that the expected dibromo compound contained 10–15% of the monobromo compound.

**Bis-(*p*-*t*-butylphenyl) ketone** was prepared by a method analogous to that reported<sup>12</sup> for benzophenone, and was used without purification or characterization.

**Bis-(*p*-*t*-butylphenyl)-dichloromethane.**—An equimolar mixture of crude bis-(*p*-*t*-butylphenyl) ketone and phosphorus pentachloride was heated to reaction and held at reflux (about 140°) for 0.5 hr. Phosphorus oxychloride was then distilled off to leave a brown solid residue. One recrystallization from hexane-petroleum ether gave a crude sample of the dichloride which was used without further purification.

All other materials were available commercially or were made by literature methods.

**(A) Reaction of Iron Pentacarbonyl with Dichlorodiphenylmethane.**—A solution of 55 ml. (0.42 mole) of dichlorodiphenylmethane in 150 ml. of benzene was refluxed while 42 ml. (0.31 mole) of iron pentacarbonyl was added dropwise during 10 minutes. During the addition the solution became dark green, carbon monoxide was evolved and a dark precipitate appeared. The mixture was refluxed (about 45 minutes) until no more gas was evolved and then was filtered hot and the precipitate washed well with benzene to obtain a yellow solution and a dark green residue. After evaporating the solvent at reduced pressure and washing the resulting solid several times with petroleum ether there remained 41.8 g. of light yellow, crude product. Two recrystallizations from acetone-water and one recrystallization from methyl ethyl ketone-ethanol removed a tenaciously held yellow contaminant and left colorless crystals of pure tetraphenylethylene, identified by its m.p. (224–226°), mixed m.p. and its infrared spectrum. The yield of crude product was 95% based on iron pentacarbonyl.

In a separate experiment a sample of the evolved gas was collected. An infrared spectrum of the gas showed the presence of carbon monoxide, benzene, iron pentacarbonyl and no others. The volume of gas given off corresponded to the evolution of five moles of carbon monoxide per mole of iron pentacarbonyl. The green precipitate contained ferrous ion, chloride ion and organic tars.

**Reaction of Iron Pentacarbonyl with Bis-(*p*-chlorophenyl)-dichloromethane.**—The reaction was carried out as in (A), and the resulting mixture was filtered. Evaporation of the filtrate at reduced pressure and crystallization of the resulting residue from chloroform-ethanol gave an 85% yield of crude product. Recrystallization of the product from the same solvent gave white needles of tetrakis-(*p*-chlorophenyl)-ethylene, m.p. 220–222° (lit.<sup>13</sup> m.p. 216–217°).

*Anal.* Calcd. for C<sub>26</sub>H<sub>16</sub>Cl<sub>4</sub>: C, 66.13; H, 3.41; Cl, 30.46. Found: C, 66.36; H, 3.44; Cl, 30.09.

**Reaction of Iron Pentacarbonyl with Bis-(*p*-nitrophenyl)-dibromomethane.**—The reaction was conducted as in (A) and the resulting brown mixture was filtered. The filtrate was evaporated to a light brown mushy solid which was first

(8) B. Hock and H. Stuhlmann, *Ber.*, **62**, 431 (1929).

(9) W. E. Catlin and J. C. Thomas, U. S. Patent 2,810,736 (1957).

(10) B. Nicholls and M. C. Whiting, *Proc. Chem. Soc.*, 152 (1958).

(11) W. Hieber and E. Romberg, *Z. anorg. allgem. Chem.*, **221**, 349 (1935).

(12) C. S. Marvel and W. M. Sperry, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 95.

(13) J. F. Norris, R. Thomas and B. M. Brown, *Ber.*, **43**, 2954 (1910).

washed well with hot ethanol and then crystallized from methyl ethyl ketone-methanol to obtain a 47% yield of yellow crystals. Recrystallization from the same solvent gave stout yellow needles, m.p. 303–304.5°, of tetrakis-(*p*-nitrophenyl)-ethylene.

*Anal.* Calcd. for  $C_{26}H_{18}N_4O_8$ : C, 61.0; H, 3.2; N, 10.9. Found: C, 61.2; H, 3.7; N, 11.3.

**Reaction of Iron Pentacarbonyl with Bis-(*p*-tolyl)-dichloromethane.**—As in (A), the reaction gave a mixture which was filtered and the filtrate evaporated under reduced pressure to a clear yellow oil. The oil was extracted with acetic acid and this hot solution was treated with water and allowed to cool to precipitate a yellow, amorphous solid. The filtrate was heated to boiling and again treated with water and cooled to produce a lighter yellow solid. The filtrate from the second fraction was subjected to the same process to produce a third fraction of light yellow material. Crystallization of the third fraction was achieved by taking the solid up in boiling petroleum ether and cooling the solution to  $-80^\circ$ . A recrystallization from acetone-water gave an oily suspension which, on standing for 12 hr., crystallized as colorless needles of tetrakis-(*p*-tolyl)-ethylene, m.p. 150–150.5° (lit.<sup>14</sup> m.p. 151°).

*Anal.* Calcd. for  $C_{10}H_{12}$ : C, 92.74; H, 7.26. Found: C, 92.82; H, 7.33.

**Reaction of Iron Pentacarbonyl with Bis-(*p*-*t*-butylphenyl)-dichloromethane.**—The reaction was carried out as in (A). Evaporation of the filtered solution gave a light brown solid which was cleaned by boiling in acetone with activated charcoal and then precipitated by addition of water. Three recrystallizations from chloroform-methanol gave very light yellow crystals of tetrakis-(*p*-*t*-butylphenyl)-ethylene. The compound melted at 350–352° with rapid sublimation.

*Anal.* Calcd. for  $C_{22}H_{28}$ : C, 90.59; H, 9.41. Found: C, 90.35; H, 9.49.

**Reaction of Iron Pentacarbonyl with Bis-(*p*-methoxyphenyl)-dichloromethane.**—A solution of 22 g. of bis-(*p*-methoxyphenyl)-dichloromethane in 150 ml. of benzene was treated dropwise with 12 ml. of iron pentacarbonyl in 25 ml. of benzene. The solution turned deep cherry red on the first addition of carbonyl, but only a very slow evolution of gas occurred. Addition of the remainder of the iron pentacarbonyl and heating the solution to reflux gave no further change. After standing for 12 hr. at room temperature, the solution was filtered to remove a trace of solid and the filtrate was evaporated to dryness. The residue was treated with 100 ml. of methanol and 10 ml. of water and the resulting solid was filtered off and crystallized from carbon disulfide-petroleum ether to produce light pink needles mixed with colorless, cotton-like crystals. Two recrystallizations from acetone-water gave colorless needles, m.p. 184.5–186°. Reported melting points for tetrakis-(*p*-methoxyphenyl)-ethylene vary from 181–182° to 186°.<sup>15</sup>

*Anal.* Calcd. for  $C_{20}H_{20}O_4$ : C, 79.7; H, 6.20. Found: C, 80.1; H, 6.25.

**Reaction of Iron Pentacarbonyl with Dibromofluorene.**—The reaction was carried out as in (A). Filtering the solution gave a red-brown solid and a dark red solution. Addition of excess ethanol to the filtrate precipitated a red solid which was filtered off and cleaned by boiling with activated charcoal in ethanol-benzene. Evaporation of the solution to incipient crystallization and cooling to 0° gave red needles which were recrystallized from chloroform-hexane. The red, crystalline bisfluorenylidene had m.p. 190–191° (lit.<sup>16</sup> m.p. 189–190°).

An infrared spectrum of the compound showed strong bands at 3030, 1470, 1440, 1340 and 720  $cm^{-1}$ , in disagreement with a spectrum recorded<sup>17</sup> in the literature for this compound. However, the spectrum was identical with that of a sample prepared by an accepted method<sup>18</sup> and a

mixed m.p. showed no depression. As further proof, the compound was brominated to 9,9'-dibromobisfluorenyl, m.p. 239° dec. (lit.<sup>16</sup> m.p. 236° dec.).

The same reaction carried out in dioxane led to a mixture of bisfluorenylidene and 9,9'-dibromobisfluorenyl, identified by comparison with the compounds prepared above.

**Reaction of Iron Pentacarbonyl with Dichlorodiphenylmethane and Sulfur.**—A mixture of 39.5 ml. of dichlorodiphenylmethane, 100 g. of sulfur and 150 ml. of benzene was warmed to near reflux and a solution of 23.7 ml. of iron pentacarbonyl in 30 ml. of benzene was added at such a rate that reflux was maintained. After gas evolution had ceased, the green mixture was cooled to room temperature, filtered, and the residue washed well with benzene. The combined blue filtrates were evaporated under reduced pressure and the residue was extracted with 200 ml. of ether. Removal of the ether at atmospheric pressure and distillation of the residue at 110–120° (0.15 mm.) gave 10 ml. of a blue liquid which was taken up in petroleum ether and chromatographed on alumina and then crystallized from petroleum ether as blue needles of thiobenzophenone, m.p. 50–52° (lit.<sup>19</sup> m.p. 53–54°). The product gave an oxime, m.p. 139–141°; the recorded<sup>20</sup> m.p. for benzophenone oxime is 141°.

**Reaction of Iron Pentacarbonyl with Diethyl Dibromomalonate.**—One-half of a solution of 28 ml. of iron pentacarbonyl in 50 ml. of benzene was added to a stirred solution of 63.0 g. of diethyl dibromomalonate in 500 ml. of benzene at room temperature. The solution darkened to orange in color and then went through brown to green-black and, as heat was applied externally, turned a deep purple color with vigorous evolution of carbon monoxide. The reaction was controlled by applying an ice-bath to the reaction flask. When the reaction had subsided, the remainder of the iron pentacarbonyl was added and the reaction again controlled by heating or cooling the solution as required. The resulting purple mixture was refluxed 0.5 hr., cooled, filtered under nitrogen, and the insoluble residue was washed with benzene until the washings were no longer purple. After drying *in vacuo*, the orange-red residue of impure ferrous bromide weighed 29.7 g.

Removal of the benzene and excess iron pentacarbonyl from the combined purple filtrates at reduced pressure left 47.0 g. of a purple, semi-crystalline mass. Purification was best accomplished by passing a petroleum ether solution of the compound through a 10-cm. column of cellulose powder, concentrating the resulting solution and cooling to  $-80^\circ$ . This procedure gave large, almost black crystals, m.p. 115–117.5° (dec. 130°).

*Anal.* Calcd. for  $Fe[BrC(COOC_2H_5)_2]_3$ : C, 32.75; H, 3.9; Br, 31.1; Fe, 7.2. Found: C, 33.2; H, 4.2; Br, 31.2; Fe, 6.6.

The compound was soluble in non-polar organic solvents, insoluble in water and decomposed by alcohols and bases. Boiling the compound in benzene with moist charcoal gave ferric hydroxide and diethyl bromomalonate.

**Reaction of Iron Pentacarbonyl with Dibromomalononitrile.**—Iron pentacarbonyl (105 ml., 0.78 mole) was added dropwise during 1.5 hr. to a solution of dibromomalononitrile (170 g., 0.75 mole) in 1 liter of ethanol at 5°. The resulting red-brown solution was stirred for 0.5 hr. at 5° and then for 2 hr. at room temperature and finally poured into 1 liter of water. After the initial foaming had subsided the solution was concentrated to 1 liter. On standing overnight the solution deposited 12.7 g. of a yellow, crystalline compound which was filtered off, washed well with water, ethanol, and then ether, and dried in air. Chemical analysis gave the empirical formula  $FeC_{12}H_{14}N_4O_6$ .

The compound was insoluble in water and organic solvents. A magnetic moment of  $5.1 \pm 0.2$  Bohr magnetons indicated a ferrous salt. Boiling the salt (2.96 g.) in concentrated ammonium hydroxide, followed by filtration of the precipitated ferrous hydroxide and evaporation of the filtrate to dryness, gave an ammonium salt (2.23 g.) which crystallized from methyl ethyl ketone as white needles, m.p. 213° dec. Treatment of this salt with concentrated

(19) H. Staudinger and H. Freudenberger, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 573.

(20) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," Third Edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 264.

(14) H. Staudinger and J. Goldstein, *Ber.*, **49**, 1925 (1916).

(15) A. Schönberg, O. Schutz and S. Nickel, *ibid.*, **61**, 1384 (1928).

(16) C. K. Ingold and J. A. Jessop, *J. Chem. Soc.*, 2380 (1929).

(17) L. Lecomte, *Publ. sci. et tech. ministere air (France)*, No. 34 (1933). Quoted in "Elsevier's Encyclopedia of Organic Chemistry," E. Josephy and F. Radt, Editors, Series III, Vol. 13, Elsevier Press, New York, N. Y., 1946, p. 123.

(18) From 9,9-dibromofluorene by a method analogous to that given by R. E. Buckles and G. M. Matlack, *Org. Syntheses*, **31**, 104 (1951).

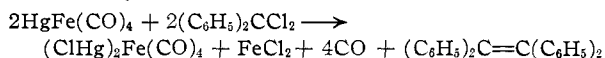
hydrochloric acid gave silky needles of an acid, m.p. 173°, which was identified as the addition product<sup>6</sup> of HCl with ethyl dicyanoacetate by direct comparison with an authentic sample.<sup>21</sup>

Thus, the original compound was the dihydrated ferrous salt of ethyl dicyanoacetate. Similarly, the dihydrate of the ferrous salt of methyl dicyanoacetate resulted when the reaction was carried out as described above with methanol as solvent.

**Reaction of Mercury Iron Tetracarbonyl with Dichlorodiphenylmethane.**—Mercury iron tetracarbonyl (3.68 g., 0.01 mole) and dichlorodiphenylmethane (2.37 g., 0.01 mole) were refluxed in 50 ml. of benzene for 0.5 hr. The resulting green solution was filtered to obtain 3.57 g. of light green insoluble residue. The residue contained a water-soluble fraction which was identified as ferrous chloride by qualitative tests, and a water-insoluble fraction which was shown to be  $(\text{C}_6\text{H}_5)_2\text{Fe}(\text{CO})_4$  by comparison of its

infrared spectrum with a spectrum of authentic material, and by thermally decomposing the compound to ferrous chloride, mercury and the theoretical amount of carbon monoxide. The original green filtrate was evaporated to dryness and the residue washed with hexane to produce 1.11 g. (0.0033 mole) of tetraphenylethylene, identified by comparison with an authentic sample.

A separate experiment was carried out as above and the liberated carbon monoxide was collected. A total of 0.018 mole of carbon monoxide was evolved. The reaction is described by



**Reaction of Other Metal Carbonyls with Dichlorodiphenylmethane.**—In each case the metal carbonyl was refluxed with dichlorodiphenylmethane in benzene for 0.5–3 hr. If any reaction had occurred, as evidenced by color changes or formation of a precipitate, the solution was filtered and the filtrate searched for organic products.

(21) Kindly supplied by Dr. W. J. Middleton.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY, CALIFORNIA]

## Structure of the Ferrichrome Compounds<sup>1,2</sup>

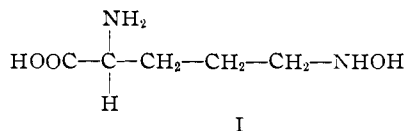
BY THOMAS EMERY AND J. B. NEILANDS

RECEIVED SEPTEMBER 24, 1960

The hydroxyamino moiety of the ferrichrome compounds has been characterized as L-2-amino-5-hydroxyaminovaleric acid ( $\delta$ -N-hydroxy-L-ornithine). Both ferrichrome and ferrichrome A contain three residues of this new amino acid which together with three residues of glycine (ferrichrome) and one residue of glycine plus two residues of serine (ferrichrome A) are contained within a cyclic hexapeptide. Tentative total structures for the ferrichrome compounds have been proposed.

In previous communications, the ferrichrome compounds were described as naturally-occurring *ferric hydroxamates*<sup>3</sup> and the acyl moieties<sup>4</sup> of the hydroxamate functions were shown to be three residues each of acetic and *trans*- $\beta$ -methylglutaconic acids for ferrichrome and ferrichrome A, respectively. The present report is concerned with the hydroxyamino functions and, in addition, tentative structures of the entire compounds are proposed which accommodate all of the characterization data including the elementary analyses (Fig. 1).

In the structure illustrated in Fig. 1, the three hydroxyamino functions are shown to be provided by three residues of 2-amino-5-hydroxyaminovaleric acid ( $\delta$ -N-hydroxyornithine, I). The prop-



erties of this new amino acid closely parallel those of the next higher homolog which was isolated from mycobactin in an elegant investigation by Snow.<sup>5</sup> Although substance I has not been obtained from the ferrichrome compounds in analyzable quantities, the existence and structure of this product are strongly inferred from the following evidence.

Vigorous acid hydrolysis of the ferrichromes always yielded variable amounts of ornithine,

(1) Abstracted from the doctoral dissertation of Thomas Emery, University of California, Berkeley, 1960.

(2) This research was sustained by a grant from the Office of Naval Research.

(3) T. Emery and J. B. Neilands, *Nature*, **184**, 1632 (1959).

(4) T. Emery and J. B. Neilands, *J. Am. Chem. Soc.*, **82**, 3658 (1960).

(5) G. A. Snow, *J. Chem. Soc.*, 2588 (1954).

usually 0.3–0.6 mole, in addition to glycine (ferrichrome) and glycine plus serine (ferrichrome A). Quantitative analysis of the hydrolysate of *iron-free* ferrichrome revealed the presence of three moles of glycine; the corresponding values for ferrichrome A were one mole of glycine and two moles of serine. No ornithine was found in hydrolysates from iron-free samples of either compound. However, three moles of I was now present. Apparently I is completely destroyed on acid hydrolysis in the presence of iron and gives rise to variable amounts of ornithine. At pH 4.9 I displayed a cationic mobility on paper electrophoresis which was intermediate between that of the neutral amino acids and ornithine. It was stained blue with ninhydrin and gave an immediate red color with the tetrazolium spray employed by Snow<sup>5</sup> for detection of the hydroxyamino grouping. Substance I was eluted from paper electrophoretograms and reduced with H<sub>2</sub> and PtO<sub>2</sub> to an amino acid which could be identified as ornithine. Alternatively, direct reductive hydrolysis of the iron-free ferrichromes with HI yielded three moles of L-ornithine. The configuration of the latter was established by quantitative growth tests with *E. coli* 160-37<sup>6</sup> which in turn indicated the asymmetric form of the parent hydroxyamino acid.

The amino acid sequence of ferrichrome shown in Fig. 1 is  $\text{[Gly-Gly-Orn(NHOH)-Orn(NHOH)-}$

$\text{Gly-Orn(NHOH)]}$ . The amino acid sequence is

tentative and is based on the examination of molecular models. The three hydroxamic acid functions must be made to satisfy the six octahedrally directed

(6) H. J. Vogel, *Proc. Natl. Acad. Sci. U. S.*, **39**, 578 (1953).