

are somewhat higher than expected, indicating some heme-heme interaction; it is possible, on the other hand, that the orbital contribution is greater than usual.

None, or one, or two of the $3d$ orbitals of trivalent iron atom in a complex may be involved in covalent bond formation, the number of unpaired electrons being five, three, or one, respectively, and the moment 5.92, about 4.2, or about 2.0 Bohr magnetons. Many complexes of the first type and many of the third type are known, whereas iron complexes of the intermediate type are very rare.²¹ Ferrihemoglobin hydroxide apparently is of this type; the observed effective moment 4.47 is only slightly larger than that expected for three unpaired electrons (spin moment 3.88, orbital contribution about 0.4).

The nature of the bonds in this complex is somewhat uncertain, since, although the value of the magnetic moment is that which is associated with square coordination (as in nickel protoporphyrin¹), there is little doubt that the configuration about the iron atom is octahedral. Four dsp^2 covalent bonds directed to the corners of a square would utilize one d orbital; in ferri-

(21) Measurements of χ made by L. Cambi and A. Cagnasso, *Rend. Ist. Lombardo Sci.*, **67**, 741 (1934), for complexes of $\text{Fe}(\text{CNS})_2$ and $\text{Co}(\text{CN})_2$ with *o*-phenanthroline and 2,2'-bipyridyl indicate structures of this type.

hemoglobin hydroxide it is probable that these four covalent bonds resonate among the six adjacent atoms, each of which is then attached to the iron atom by a bond with roughly two-thirds covalent character (or perhaps somewhat less).

Summary

Magnetic measurements at approximately 24° of solutions of ferrihemoglobin and some of its compounds have been made, leading to values of the paramagnetic part of the molal susceptibility which correspond to the following values of the effective magnetic moment per heme, in Bohr magnetons: ferrihemoglobin, 5.80; ferrihemoglobin hydroxide, 4.47; ferrihemoglobin fluoride, 5.92; ferrihemoglobin cyanide, 2.50; ferrihemoglobin hydrosulfide, 2.26. For ferrihemoglobin and its fluoride these correspond to five unpaired electrons per heme, indicating essentially ionic bonds; for the cyanide and hydrosulfide to one, indicating essentially covalent bonds; and for the hydroxide to three, indicating bonds of an intermediate type.

Values determined by magnetic titrations are reported for the dissociation constants of ferrihemoglobin hydroxide, fluoride and cyanide.

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Arsonated Derivatives of Mixed Ketones

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In a study of arsonated aliphatic-aromatic ketones¹⁻⁴ a number of attempts were made to condense *p*-hydroxyphenylarsonic acid with nitriles in various solvents with and without catalysts. There was no evidence of condensation in any case, results which were not entirely unexpected in view of the fact that the literature does not report condensations with nitrophenols and hydroxybenzenesulfonic acids.

Although direct arsonation of resorcinol⁵ gives good yields of resorcinol arsonic acid, 2,4-dihydroxyacetophenone⁶ and the corresponding pro-

piophenone derivative did not react with arsenic acid to form more than traces of the arsonic acids. Protection of the phenolic hydroxyl groups by acetylation⁷ or methylation⁸ before heating with arsenic acid failed to give any arsonic acid although a few instances of direct arsonation of compounds containing no free hydroxyl groups are recorded.⁵ Methylation of the products before their separation from the reaction mixture gave 10% yields.

The introduction of arsenic into hydroxyaromatic-aliphatic ketones through the diazo reaction⁹ was exceedingly difficult. Attempts to condense *p*-nitrophenol and nitroresorcinol¹⁰ with

(1) Lewis and Cheetham, *THIS JOURNAL*, **43**, 2117 (1921).
 (2) Lewis and Cheetham, *ibid.*, **45**, 510 (1923).
 (3) Deutsche Gold- und Silber-Scheideanstalt vorm. Roessler, Austrian Patent 100,211 (1922).
 (4) Margulies, British Patent 220,668 (1923).
 (5) Bauer, *Ber.*, **48**, 509 (1915).
 (6) Hoesch, *ibid.*, **48**, 1122 (1915).

(7) Brüll and Friedlaender, *ibid.*, **30**, 297 (1897).
 (8) Perkin, Robinson and Turner, *J. Chem. Soc.*, **93**, 1085 (1908).
 (9) Bart, *Ann.*, **429**, 55 (1922).
 (10) Kauffmann and Kügel, *Ber.*, **44**, 753 (1911).

nitriles proving unsuccessful, it was found necessary to prepare the amines of the hydroxy ketones for use in the diazotization from 2,4-dihydroxyacetophenone and the corresponding propiophenone derivative by nitration and reduction of the nitro compounds. The instability of the resulting amines required their isolation as amine hydrochlorides. The same sort of difficulty was encountered in arsonation through the diazo reaction as in direct arsonation. Both 2,4-dihydroxy-5-aminoacetophenone and 2,4-dihydroxy-5-aminopropiophenone were easily diazotized; but, under the wide variety of conditions tried, no more than a very small amount of an unstable impure material showing arsonation could be obtained.

However, methylation of the hydroxyl groups in 2,4-dihydroxy-5-nitroacetophenone and the corresponding propiophenone derivative resulted in very stable compounds. These were reduced catalytically and the somewhat unstable amines isolated through their hydrochlorides. Arsonation of these compounds proceeded easily, giving good yields of 2,4-dimethoxy-5-arsonoacetophenone and 2,4-dimethoxy-5-arsonopropiophenone.

Experimental

2,4-Dihydroxypropiophenone.^{11,12}—Prepared from resorcinol and propionitrile by a method similar to that used by Hoesch in making 2,4-dihydroxyacetophenone⁶; yield 65%.

2,4-Dimethoxypropiophenone.—From 2,4-dihydroxypropiophenone following the method of Perkin, Robinson and Turner.⁸ The yellow oily solid thus obtained was recrystallized twice from 50% ethyl alcohol solution, giving a white solid with a pleasant ethereal odor; m. p. 67°; 68% yield.

Anal. Calcd. for C₁₁H₁₄O₃: C, 68.00; H, 7.21. Found: C, 67.93, 67.76; H, 7.22, 7.21.

2,4-Dihydroxy-5-nitroacetophenone.—Fifty grams of 2,4-dihydroxyacetophenone was added in small portions with constant stirring to 400 cc. of nitric acid (1.42) cooled in an ice-bath. The addition was carried on at such a rate that each portion of the solid was dissolved completely before the next was introduced and so that the temperature remained below 10°. The stirring was continued for an hour, during which time a dark red solid separated, and the mixture then poured into a 2-liter beaker half full of chipped ice. The nitro compound was filtered out, washed with water and boiled with 500-cc. portions of water until all of the red color had been removed. The light yellow solid was then filtered out, dried and recrystallized from ethyl alcohol, giving 46 g. of the mononitro derivative; m. p. 142°.

(11) Nencki and Schmid, *J. prakt. Chem.*, **23**, 546 (1881).

(12) Brewster and Harris, *THIS JOURNAL*, **52**, 4866 (1930).

Anal. Calcd. for C₈H₇O₃N: N, 7.11. Found: N, 7.13, 7.12.

2,4-Dihydroxy-5-nitropropiophenone.—Nitration of 2,4-dihydroxypropiophenone by a procedure similar to that used with the corresponding acetophenone derivative gave a 77% yield of the white nitro compound; m. p. 131°.

Anal. Calcd. for C₉H₉O₃N: N, 6.64. Found: N, 6.68, 6.66.

2,4-Diacetoxy-5-nitropropiophenone.—From 2,4-dihydroxy-5-nitropropiophenone by the method of Brüll and Friedlaender.⁷ Recrystallization from carbon tetrachloride gave a 90% yield of the cream colored product; m. p. 89°.

Anal. Calcd. for C₁₃H₁₃O₇N: N, 4.98. Found: N, 5.04, 4.92.

2,4-Dimethoxy-5-nitroacetophenone.—Nineteen and seven-tenths grams of 2,4-dihydroxy-5-nitroacetophenone was dissolved in 33 cc. of 20% sodium hydroxide solution. To this solution in a 250-cc. flask was added 30 cc. of dimethyl sulfate. The mixture was stirred thoroughly, heated gently until the strongly exothermic reaction started and shaken until cool. The solid brown cake which formed was filtered out and ground up in *N* sodium carbonate solution to remove any material not entirely methylated. The solid remaining was filtered out, washed thoroughly with water, dried and recrystallized from hot ethyl alcohol; yield 15.5 g. of a finely divided cream colored product; m. p. 177°.

Anal. Calcd. for C₁₀H₁₁O₅N: N, 6.22. Found: N, 6.32, 6.25.

2,4-Dimethoxy-5-nitropropiophenone.—By a procedure similar to that used with 2,4-dihydroxy-5-nitroacetophenone, a 75% yield of cream colored dimethoxy derivative, m. p. 155°, was obtained.

Anal. Calcd. for C₁₁H₁₃O₅N: N, 6.70. Found: N, 6.64, 6.81.

Amine Hydrochlorides

General Procedure.—The hydrochloride of the amine was prepared from the corresponding nitro compound by catalytic reduction¹³ in acetone solution using Raney catalyst.¹⁴ At the end of the reaction the catalyst was filtered out, half the acetone removed by distillation under reduced pressure, and the hydrochloride prepared by passing dry hydrogen chloride into the remaining solution. In cases where the hydrochloride was somewhat soluble in acetone, ether was added to throw it out. The amine hydrochloride was filtered out, dried and recrystallized from

TABLE I

Hydrochloride of	Formula	Nitrogen analyses, %		
		Calcd.	Found	
2,4-Dihydroxy-5-aminoacetophenone	C ₈ H ₇ O ₃ NCl	6.88	6.68	6.77
2,4-Dihydroxy-5-aminopropiophenone	C ₉ H ₉ O ₃ NCl	6.44	6.31	6.33
2,4-Dimethoxy-5-aminoacetophenone	C ₁₀ H ₁₁ O ₅ NCl	6.05	5.95	5.92
2,4-Dimethoxy-5-aminopropiophenone	C ₁₁ H ₁₃ O ₅ NCl	5.70	5.61	5.60

(13) Stevinson and Hamilton, *THIS JOURNAL*, **57**, 1298 (1935).

(14) Raney, U. S. Patent 1,628,190 (1927).

alcohol, giving nearly quantitative yields of finely divided solid which was not melted at 300°.

Amines

General Procedure.—The amines were prepared from the corresponding amine hydrochlorides by addition of *N* sodium carbonate solution.

TABLE II

	M. p., °C.	Formula	Nitrogen analyses, %		
			Calcd.	Found	
2,4-Dihydroxy-5-aminoacetophenone	137–142 ^a	C ₈ H ₈ O ₃ N	8.38	8.19	8.21
2,4-Dihydroxy-5-aminopropiophenone	147–151 ^a	C ₉ H ₁₁ O ₃ N	7.74	7.58	7.61
2,4-Dimethoxy-5-aminoacetophenone	114	C ₁₀ H ₁₂ O ₃ N	7.18	7.34	7.28
2,4-Dimethoxy-5-aminopropiophenone	107	C ₁₁ H ₁₄ O ₃ N	6.70	6.84	6.81

^a With decomposition.

2,4-Dimethoxy-5-arsonoacetophenone.—(a) 2,4-Dimethoxy-5-arsonoacetophenone was prepared from the hydrochloride of 2,4-dimethoxy-5-aminoacetophenone by diazotization followed by coupling with sodium arsenite. Twenty-three and a half grams of the amine hydrochloride was dissolved in water and 16.5 cc. of 12 *N* hydrochloric acid added. This was cooled to 0° and diazotized by adding slowly 105 cc. of *N* sodium nitrite solution. The resulting solution was stirred for an additional fifteen minutes, cooled, and 20 cc. of 5 *N* sodium hydroxide solution stirred in, followed at once by a mixture containing 75 cc. of 2 *N* disodium monohydrogen arsenite solution, 2.5 cc. of 12 *N* hydrochloric acid, 200 cc. of water, 200 cc. of ice and 40 cc. of 10% copper sulfate solution. Nitrogen was evolved rapidly, and a few cc. of ethyl acetate was added to prevent excessive foaming. The reaction mixture was stirred for three hours, and, after standing overnight, it was heated to 50–60° on a steam-bath and filtered. The filtrate was made acid to litmus with acetic acid and concentrated to half its former volume on a steam-bath. The mixture was filtered twice through a charcoal filter to remove the color. On making the filtrate acid to Congo red paper with hydrochloric acid, the white arsonic acid separated. It was filtered out, washed, dried and purified by recrystallizing twice from "cellosolve"; yield 17 g.; m. p. 250°.

(b) Methylation of the reaction mixture obtained on heating 2,4-dihydroxyacetophenone and arsenic acid for five hours at 150–155° gave a 7% yield of 2,4-dimethoxy-5-arsonoacetophenone.

*Anal.*¹⁵ Calcd. for C₁₀H₁₂O₃As: As, 24.35. Found: As, 24.30, 24.32.

2,4-Dimethoxy-5-arsonopropiophenone.—(a) A 61% yield of 2,4-dimethoxy-5-arsonopropiophenone was obtained from 2,4-dimethoxy-5-aminopropiophenone through the diazo reaction and coupling with sodium arsenite; m. p. 243°. (b) Methylation of the reaction mixture from the direct arsonation of 2,4-dihydroxypropyphenone by heating with arsenic acid for seventy-five hours at 100° gave an 11% yield of 2,4-dimethoxy-5-arsonopropiophenone.

Anal. Calcd. for C₁₁H₁₄O₃As: As, 23.55. Found: As, 23.42, 23.44.

Summary

1. 2,4-Dimethoxy-5-arsonoacetophenone and 2,4-dimethoxy-5-arsonopropiophenone were prepared by diazotization of the corresponding amino derivative followed by coupling with sodium arsenite. The same compounds were formed also by methylation of the product from the direct arsonation of 2,4-dihydroxyacetophenone and 2,4-dihydroxypropyphenone.

2. 2,4-Dihydroxypropyphenone was obtained by the nuclear condensation of propionitrile and resorcinol under the conditions of a Hoesch reaction.⁶

3. Several intermediate compounds and compounds incidental to the problem were prepared and identified for the first time.

4. All attempted arsonations of 2,4-dihydroxyacetophenone and 2,4-dihydroxypropyphenone by the Bart reaction⁹ were unsuccessful.

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(15) The potentiometric method of Cislak and Hamilton [THIS JOURNAL, 52, 638 (1930)] was used for the quantitative determination of arsenic in all arsenic-containing compounds prepared.