By means of hydrolysis, decarboxylation and treatment with phosphorus oxychloride, the ethyl quinaldates were converted to the corresponding 4-chloro-3-halo derivatives which were condensed with 4-diethylamino-1-methylbutylamine. Reductive dehalogenation which occurred in the attempts to condense the 4-chloro-3-iodoquinolines with 4-diethylamino-1-methylbutylamine is reported. These same iodoquinolines were successfully condensed with 3-diethylamino-2-hydroxypropylamine by using lower temperatures.

RENSSELAER, NEW YORK RECEIVED AUGUST 27, 1946

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

The Synthesis of Certain Substituted 2,2′-Bipyridyls[1]

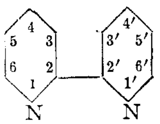
BY FRANCIS H. CASE

The compound 1,10-phenanthroline, in the form of its ferrous complex, has found important use as an indicator in volumetric analysis. Recently Richter and Smith[2] have modified the structure of this compound by the introduction of various substituents in the 5- and 6- positions of the original molecule, and observed corresponding differences in the potentials needed to oxidize the ferrous complexes.

The compound 2,2′-bipyridyl I containing the same grouping, $=N-\overset{\|}{C}-\overset{\|}{C}-N=$ as 1,10-phenanthroline, also forms a deep red-colored complex (ferroin reaction) with ferrous salts and is used extensively as a sensitive qualitative reagent for ferrous iron. As an oxidation–reduction indicator, the ferrous complex has a desirably low oxidation potential but is unfortunately relatively unstable to oxidation.

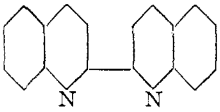
It was felt that the introduction of various substituent groups in the bipyridyl molecule might provide complexes with higher and lower oxidation potentials than those now available and also possibly increase the stability of the ferrous complex.

Up to the present time practically all substituted 2,2′-bipyridyls have contained the substituent groups either in the 6- or the 6,6′-positions.



I

These groups include bromo, amino, cyano, carboxyl and methyl. Other bipyridyls substituted in the above positions include such fused ring heterocycles as 2,2′-biquinolyl II, 2-(2′-pyridyl)-quinoline III, and 2-(2′-pyrryl)-quinoline IV.[3]



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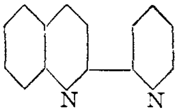

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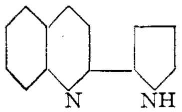


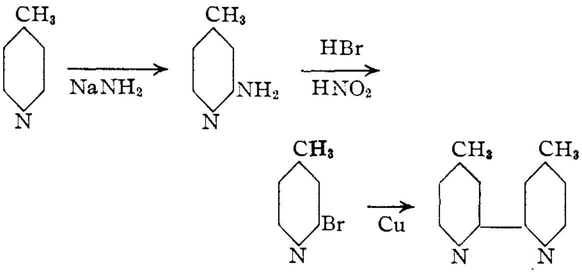
IV

It has been found that in all the above derivatives the power to form colored ferrous complexes is practically lost.

By the bromination of 2,2′-bipyridyl hydrobromide at 250° Burstall[4] obtained mono and dibromobipyridyls which he regarded as 5-bromo and 5,5′-dibromo derivatives, respectively. Proof of structure was lacking. The mono-bromo derivative gave a deep red color with ferrous sulfate, but none was afforded by the di-bromo compound.

In this Laboratory attention has been directed to the synthesis of various substituted 2,2′-bipyridyls other than the 6,6′-derivatives.

When γ-picoline was subjected to the action of anhydrous $FeCl_3$ at 320° (the method used by Hein and Retter[5] to prepare 2,2′-bipyridyl from pyridine) it was converted into 4,4′-dimethyl-2,2′-bipyridyl V. The structure of this product was confirmed by its synthesis according to the scheme



V

β-Picoline, similarly treated with sodamide, yields 2-amino-3-methylpyridine which by a similar process is converted into 3,3′-dimethyl-2,2′-bipyridyl, a high-boiling liquid.

The action of ferric chloride on β-picoline could conceivably lead to the formation of any one of three possible isomers: 3,3′-dimethyl-2,2′-bipyridyl VI, 5,5′-dimethyl-2,2′-bipyridyl VII, or 3,5′-dimethyl-2,2′-bipyridyl VIII.

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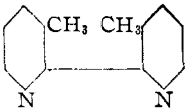
[1] Presented before the Organic Division at the Atlantic City Meeting of the American Chemical Society, April, 1946.

[2] Richter and Smith, THIS JOURNAL, **66**, 396 (1944).

[3] Smirnoff, *Helv. Chim. Acta*, **4**, 802 (1921).

[4] Burstall, *J. Chem. Soc.*, 1662 (1938).

[5] Hein and Retter, *Ber.*, **61**, 1790 (1928).



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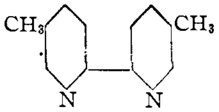

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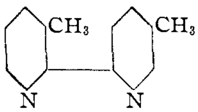
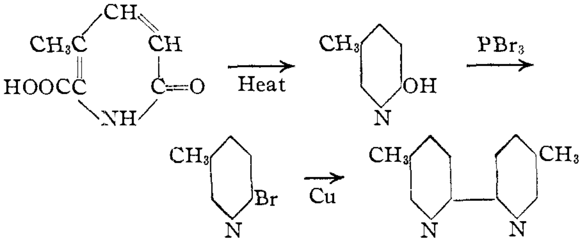


VIII

The solid product isolated from the reaction mixture was identified as the 5,5'-derivative by the following synthesis, starting with 3-methyl-6-hydroxypicolinic acid.[5a]



2-Bromo-5-methylpyridine was subsequently prepared from 2-amino-5-methylpyridine, obtained from the Reilly Tar and Chemical Corporation.

An investigation of the liquid ferric chloride reaction mixture based on its conversion to picrates and subsequent fractional crystallization indicated the formation of a small amount of 3,3'-dimethyl-2,2'-bipyridyl plus another liquid product (liberated from a picrate and as yet unidentified) which might be 3,5'-dimethyl-2,2'-bypyridyl.

In addition to the above mentioned dimethylbipyridyls, the following have also been prepared by subjecting the appropriate halide to Ullmann's reaction: 5,5'-dichloro-2,2'-bipyridyl, 5,5'-dibromo-2,2'-bipyridyl,[6] and 5,5'-dinitro-2,2'-bipyridyl. In all cases the yields were exceedingly poor. Except in the preparation of the dinitro derivative, the bromo compound was found to be the most suitable halo compound for the reaction.

By the oxidation of 4,4'- and 5,5'-dimethyl-2,2'-bipyridyl the corresponding dibasic acids were obtained.[7] These were insoluble in all solvents tried and did not melt below 360°, resembling in this respect biphenyl-4,4'-dicarboxylic acid. The dimethyl esters were prepared and characterized.

All the dimethyl bipyridyls and the crude dicarboxylic acids give a deep red color with ferrous sulfate; the dimethyl ester of the 4,4'-dicarboxylic acid gives a faint red color; none is given by the 5,5'-dimethyl ester or by the dichloro, dibromo, or dinitro derivatives.

The derivatives which form colored ferrous complexes are being tested as to oxidation potential and stability by G. Frederick Smith of the University of Illinois.

This work was supported, in part, by a Grant from the Committee on Research and Publication of Temple University.

Experimental

2-Bromo-3-methylpyridine.—A mixture of 55 g. of 3-methyl-2-pyridone and 180 g. of phosphorus tribromide was heated at 180–190° for three hours. After cooling, the contents of the flask was decomposed with ice water, made alkaline with sodium hydroxide, and extracted with ether. After removal of the ether the residue was vacuum-distilled, yielding 35.5 g. of a liquid boiling largely at 130° (56 mm.). On redistillation at atmospheric pressure 25 g. of liquid boiling at 205–220° was obtained; yield, 29%. The pure liquid boils at 218–219°.

Anal. Calcd. for C_6H_6NBr: Br, 46.48. Found: Br, 46.01.

2-Bromo-3-methylpyridine was also prepared directly from the amino derivative by the method used for the preparation of 2-bromo-4-methylpyridine (see later). From 41 g. of 2-amino-3-methylpyridine was obtained 30 g. of bromo compound, b. p. 215–221°; yield, 46%.

3,3'-Dimethyl-2,2'-bipyridyl.—A mixture of 18.5 g. of 2-bromo-3-methylpyridine and 29 g. of copper powder was heated to 220°, and the temperature gradually raised to 240° during the course of three-fourths of an hour. After cooling, the reaction mixture was extracted with dilute hydrochloric acid, made alkaline with a sodium hydroxide–ammonium hydroxide mixture, and extracted with ether. The residue on distillation at atmospheric pressure yielded 4 g. of a liquid boiling at 293–298°; yield, 40%.

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.21; H, 6.57. Found: C, 78.01; H, 6.78.

The picrate[8] of 3,3'-dimethyl-2,2'-bipyridyl, on crystallization from ethanol–acetone, melts at 188–189°.

Anal. Calcd. for $C_{24}H_{18}N_8O_{14}$: (dipicrate) C, 44.86; H, 2.83. Found: C, 44.98; H, 3.04.

2-Bromo-4-methylpyridine.—(The method of Craig[9] was used.) To a solution of 12 g. of 2-amino-4-methylpyridine in 70 ml. of 47% hydrobromic acid was added 17 ml. of bromine. A solution of 21 g. of sodium nitrite in 30 ml. of water was then added gradually, keeping the temperature below 5° until near the end of the reaction when it rose spontaneously to 10°. A solution of 45 g. of sodium hydroxide in 115 ml. of water was then dropped in below 25°. The resulting oil was extracted with ether and distilled *in vacuo*, b. p. 100–105° (8 mm.). On redistillation at atmospheric pressure 15 g. was obtained of a liquid boiling at 218–228°; yield, 77%. Pure 2-bromo-4-methylpyridine boils at 223–224°.

Anal. Calcd. for C_6H_6NBr: Br, 46.48. Found: Br, 46.73.

4,4'-Dimethyl-2,2'-bipyridyl. (A) From 2-Bromo-4-methylpyridine.—This was prepared in the same manner as 3,3'-dimethyl-2,2'-bipyridyl, previously described. From 12.5 g. of bromo compound was obtained 2.2 g. of 4,4'-dimethyl-2,2'-bipyridyl, m. p. 171–172° (from benzene); yield, 33%.

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.21; H, 6.57. Found: C, 78.46; H, 6.47.

(B) From γ-Picoline and Anhydrous Ferric Chloride.—Four tubes each containing 30 g. of anhydrous ferric chloride and 65 g. of γ-picoline were heated at 320° for eight hours. The contents of the tubes were then extracted with dilute hydrochloric acid, and the solution

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[5a] Fried and Elderfield, *J. Org. Chem.*, **6**, 567 (1941).

[6] Willink and Wibaut, *Rec. trav. chim.*, **54**, 275 (1935), reported their inability to obtain the expected dibromobipyridyl from the action of copper on 2,5-dibromopyridine.

[7] 2,2'-Bipyridyl-3,3'-dicarboxylic acid has already been prepared by the oxidation of 1,10-phenanthroline.

[8] All picrates described in this paper were prepared by the use of an excess over two moles of picric acid.

[9] Craig, THIS JOURNAL, **56**, 232 (1934).

made alkaline. The resulting suspension of ferrous hydroxide was extracted with ether with the aid of centrifugation. After removal of the ether, the resulting oil was distilled at atmospheric pressure. The part boiling below 260° was discarded. The remainder solidified. After crystallization from methanol, 19.7 g. of solid was obtained, m. p. 170–171°; yield, 7.7%.

The Action of Anhydrous Ferric Chloride on β-Picoline.—Four tubes each containing 30 g. of anhydrous ferric chloride and 63 ml. of β-picoline (previously purified through the zinc salt (m. p. 160)) were heated at 320–330° for nine to ten hours. The contents of the tubes were extracted with dilute hydrochloric acid, and the solution having been made alkaline, was steam distilled until the distillate gave only a faint pink color with ferrous sulfate. The combined distillate was acidified, evaporated to small volume, made alkaline, and extracted with ether. On removal of the ether the resulting oil was distilled at atmospheric pressure, yielding 29 g. boiling between 240 and 320°. After three distillations the following fractions were taken: A (b. p. 290–305°, 6.5 g.); B (b. p. 305–310°, 9.5 g.); C (b. p. 310–318°, 6 g.). From B and C on standing 3 g. of crude solid separated, which yielded 2.1 g. of pure 5,5′-dimethyl-2,2′-bipyridyl. Each fraction was separately converted to picrate and repeatedly crystallized to constant melting point. From A and B, 1.6 g. of picrate melting at 175–180° was obtained. This yielded 0.6 g. of product melting at 186–187° and unchanged when mixed with the picrate of 3,3′-dimethyl-2,2′-bipyridyl. From B and C a total of 5.7 g. of a picrate was obtained melting at 133–134°. From A only a trace of the same product was obtained.

Anal. Calcd. for $C_{18}H_{15}N_5O_7$: (monopicrate) C, 52.30; H, 3.66. Found: C, 51.86; H, 3.92.

The free base liberated from this picrate with dilute hydrochloric acid was an oil.

3-Methyl-6-hydroxypicolinic Acid.—Five grams of 5-methyl-6-carboxy-α-pyrone was heated in a sealed tube for five hours at 120–140° with 30 ml. of 28% ammonium hydroxide diluted with 24 cc. of water. After completion of the reaction the mixture was evaporated to dryness, taken up in water, and the acid precipitated by the addition of dilute hydrochloric acid. Crystallization from acetic acid yielded 2 g. of 3-methyl-6-hydroxypicolinic acid, which decomposes at 286°.

5-Methyl-2-pyridone.—A mixture of 2.3 g. of 3-methyl-6-hydroxypicolinic acid and 0.5 g. of copper powder was heated for fifteen minutes at 300°. The residue on crystallization from benzene yielded 1 g. of 5-methyl-2-pyridone, m. p. 182–183°.

Anal. Calcd. for C_6H_7ON: C, 66.02; H, 6.47. Found: C, 66.26; H, 6.67.

5-Methyl-2-bromopyridine. (a) From 5-Methyl-2-pyridone.—A mixture of 7.5 g. of 5-methyl-2-pyridone and 25 g. of phosphorus tribromide was heated for two and one-half hours at 180–190°. The reaction mixture was then poured on ice, made alkaline, and extracted with ether. The residue on vacuum distillation yielded 4.9 g. of an oil boiling at approximately 80° (7 mm.) which solidified at room temperature.

(B) From 2-Amino-5-methylpyridine.—The reaction was the same as that used in the preparation of 2-bromo-4-methylpyridine. From 45.5 g. of 2-amino-5-methylpyridine was obtained 41 g. of pure product, crystallizing from petroleum ether; m. p. 49–50°; yield, 57%.

Anal. Calcd. for C_6H_6NBr: Br, 46.48. Found: Br, 46.58.

2-Bromo-5-chloropyridine.—This was prepared from 2-amino-5-chloropyridine by the method of Craig.[9] From 14.2 g. of base was obtained 12.5 g. of pure product, crystallizing from methanol and melting at 70–71°.

Anal. Calcd. for C_5H_3NBrCl: C, 31.18; H, 1.57. Found: C, 31.11; H, 1.81.

5,5′-Dichloro-2,2′-bipyridyl.—Twenty-five grams of copper powder was added gradually with stirring to 21.5 g. of 2-bromo-5-chloropyridine keeping the temperature at 225°. After one hour the mixture set to a hard mass, which was powdered and treated with warm dilute hydrochloric acid. The mixture was then made alkaline with sodium hydroxide, the entire residue dried and extracted with acetone. After removal of acetone the resulting solid was crystallized from ethanol, yielding 1 g. of solid, melting at 199–200°; yield, 8%.

Anal. Calcd. for $C_{10}H_6N_2Cl_2$: Cl, 31.52. Found: Cl, 31.43.

2-Amino-5-bromopyridine.—The following method, was found more convenient than those previously described: To a solution of 18.8 g. of 2-aminopyridine in 200 ml. of ethanol 40 g. of bromine was added gradually, keeping the temperature below 20°. After removal of ethanol, the residue was made alkaline with sodium hydroxide and extracted with ether. The ether residue was extracted twice with petroleum ether to remove dibromoaminopyridine and then crystallized from benzene. The yield was 16 g., m. p. 137–138°; yield, 46%.

2,5-Dibromopyridine.—This was prepared from 2-amino-5-bromopyridine by the method of Craig. From 30 g. of base was obtained 31 g. of pure product, m. p. 96–97°.

5,5′-Dibromo-2,2′-bipyridyl.—The method of preparation was similar to that used for the dichloro derivative. From 29 g. of 2,5-dibromopyridine and 35 g. of copper was obtained 0.2 g. of pure product, melting at 224–225° when crystallized from ethanol.

Anal. Calcd. for $C_{10}H_6N_2Br_2$: Br, 50.92. Found: Br, 51.36.

Burstall[4] reports m. p. 212–213° for the product obtained by dibrominating 2,2′-bipyridyl.

2-Iodo-5-nitropyridine.—A solution of 23.4 g. of 2-amino-5-nitropyridine in 140 ml. of 50% acetic acid was added to a boiling solution of 14 g. of sodium nitrite and 30 g. of potassium iodide in 120 ml. of water. After one hour of standing the mixture was made alkaline with sodium hydroxide, treated with sodium bisulfite solution, and filtered. The precipitate was crystallized from ethanol–acetone; yield, 6 g. (14%), m. p. 165–166°.

Anal. Calcd. for $C_5H_3N_2O_2I$: I, 50.78. Found: I, 50.70.

5,5′-Dinitro-2,2′-bipyridyl.—To a stirred solution of 18 g. of 5-nitro-2-iodopyridine in 22 ml. of cymene was added 18 g. of copper powder and the temperature maintained at 180° for one hour. The mixture was then acidified with hydrochloric acid, and the cymene removed by steam distillation. After the residue had been made alkaline, the precipitate was filtered off, dried, and extracted with acetone. The residue (0.2 g.) on crystallization from acetone, melts at 244–245°.

Anal. Calcd. for $C_{10}H_6N_4O_4$: C, 48.77; H, 2.46. Found: C, 49.04; H, 2.89.

Dimethyl-2,2′-bipyridyl-4,4′-dicarboxylate.—To a solution of 22 g. of potassium permanganate in 380 ml. of water was added 4 g. of 4,4′-dimethyl-2,2′-bipyridyl, and the mixture heated to decolorization of the permanganate. After removal of the precipitated manganese dioxide the filtrate was extracted with ether to remove unchanged 4,4′-dimethyl-2,2′-bipyridyl, and acidified with hydrochloric acid. The crude acid (2.7 g.) thus obtained was found, after drying, to be insoluble in all the usual solvents. It did not melt below 360°. By refluxing with methanol in the presence of concentrated sulfuric acid it was converted to the dimethyl ester. This substance, after crystallization from methanol, melts at 210–211°.

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.74; H, 4.45. Found: C, 61.70; H, 4.64.

Dimethyl-2,2′-bipyridyl-5,5′-dicarboxylate.—Oxidation of 4 g. of 5,5′-dimethyl-2,2′-bipyridyl as above yielded 4.5 g. of crude acid which was insoluble in all the usual solvents and did not melt below 360°. The dimethyl ester, crystallized from dioxane, melts at 261–262°.

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.74; H, 4.45. Found: C, 61.80; H, 4.71.

Summary

1. The synthesis of 3,3′-, 4,4′-, and 5,5′-dimethyl-2,2′-bipyridyls is described.

2. 2,2′-Bipyridyl-4,4′- and 5,5′-dicarboxylic acids and their methyl esters have been prepared.

3. The synthesis of 5,5′-dinitro, dichloro and dibromo-2,2′-bipyridyls is described.

4. The ferroin reaction is given by the compounds mentioned in (1), by the acids in (2), but not by the compounds in (3).

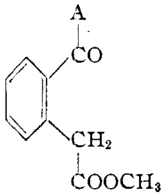
PHILADELPHIA, PENNA. RECEIVED SEPTEMBER 6, 1946

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

1,2,5,6-Dibenzcycloöctatetraene[1]

BY LOUIS F. FIESER AND MAURICE M. PECHET

In a previous investigation[2] directed toward the further elucidation of the character of the cyclooctatetraene ring a nine-step process was worked out for the preparation of benzcycloöctanol-3, a possible intermediate for the synthesis of the as yet unknown benzcycloöctatetraene. In this continuation of the research an attempt was first made to dehydrate the alcohol by cleavage of the tosylate, but with discouraging results. Various condensation reactions that might afford benzo derivatives of cycloöctatetraene were then explored. Homophthalic acid was prepared by a very convenient process consisting in the chromic acid oxidation of indene (60% yield) and converted into the known half ester I (A = OH) with the idea that the corresponding ester-aldehyde (I, A = H) might be obtained and condensed to dicarbethoxydibenzcyclooctatetraene. However, all attempts to prepare the acid chloride preliminary to Rosenmund reduction led merely to the production of the known 3-chloroisocoumarin, II. The next trial was based upon the work of Thiele and Schneider,[3] who condensed phthalaldehyde with acetonedicarboxylic ester and obtained benzcycloheptadienone dicarboxylic ester in good yield. We investigated the condensation of homophthalaldehyde with acetone dicarboxylic ester but isolated only known products of the self-condensation of each component.



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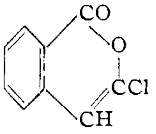

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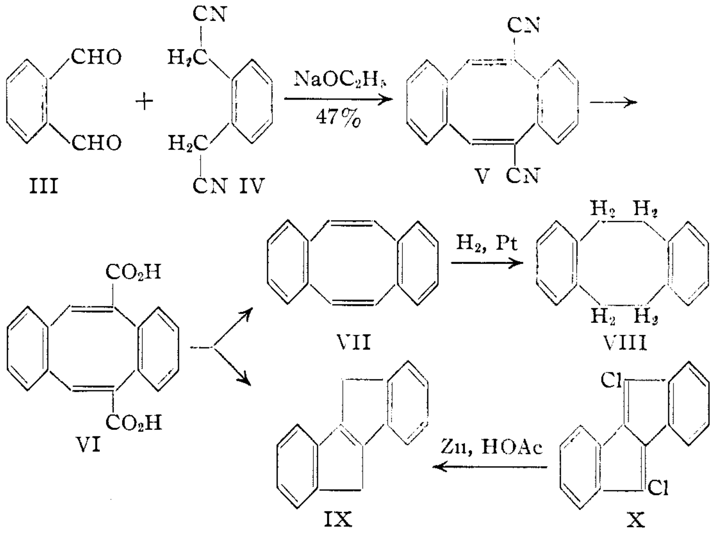

A successful synthesis was finally found in the condensation of *o*-phthaldehyde (III) with *o*-phenylenediacetonitrile (IV) in the presence of sodium ethoxide. A white substance having the composition of the expected 3,8-dicyano-1,2,5,6-dibenzcycloöctatetraene (V) was isolated in moderate yield along with a bright red by-product. The white substance on hydrolysis with 50% sulfuric acid yielded a half amide of the dibasic acid and on alcoholysis gave chiefly the diester, along with a little monoester. The diacid (VI) was obtained readily from the diester, but the decarboxylation step went poorly under the best of several conditions tried. In most experiments two isomeric hydrocarbons were formed, neither of which could be converted into the other. The higher melting, less soluble isomer corresponded in properties to the known diphenylsuccindene-10 (IX) and proved to be identical with a sample prepared by reduction of 9,10-dichlorodiphenylsuccindadiene[4] (X). The other hydrocarbon, a colorless substance of the formula $C_{16}H_{16}$ and melting at 107–108°, decolorized permanganate and bromine solutions in the cold, and in the presence of catalyst absorbed two moles of hydrogen and gave a hydrocarbon that did not depress the

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[1] The results of this investigation were described in the doctoral dissertation of Maurice M. Pechet, February 1, 1944; a preliminary report of the work was presented at the Detroit meeting of the American Chemical Society.

[2] Fry and Fieser, THIS JOURNAL, **62**, 3489 (1940).

[3] Thiele and Schneider, *Ann.*, **369**, 294 (1909).

[4] Brand and Müller, *Ber.*, **55**, 601 (1922).