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[Contribution from the Department of Chemistry, Duke University]

Aminomethylation of Ferrocene to Form *N,N*-Dimethylaminomethylferrocene and Its Conversion to the Corresponding Alcohol and Aldehyde[1]

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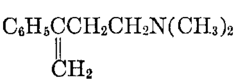
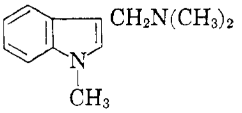
Ferrocene was aminomethylated with formaldehyde and dimethylamine in glacial acetic acid to form *N,N*-dimethylaminomethylferrocene, the methiodide of which was converted by sodium hydroxide to hydroxymethylferrocene. This primary alcohol was oxidized with manganese dioxide to the corresponding aldehyde without affecting the iron in the molecule which is known to be sensitive to oxidation. Appropriate derivatives of the alcohol and aldehyde were prepared.

It has previously been shown that certain reactive olefins and aromatic compounds can be aminomethylated with formaldehyde and dimethylamine in the presence of acid. For example, α-methylstyrene and 1-methylindole can be condensed with these reactants to form I[2] and II,[3] respectively. These reactions are somewhat similar to both the Prins addition of formaldehyde to olefins[4] and to the Mannich type of aminomethylation of methyl ketones.[5]



$C_6H_5\underset{\underset{CH_2}{\|}}{C}CH_2CH_2N(CH_3)_2$

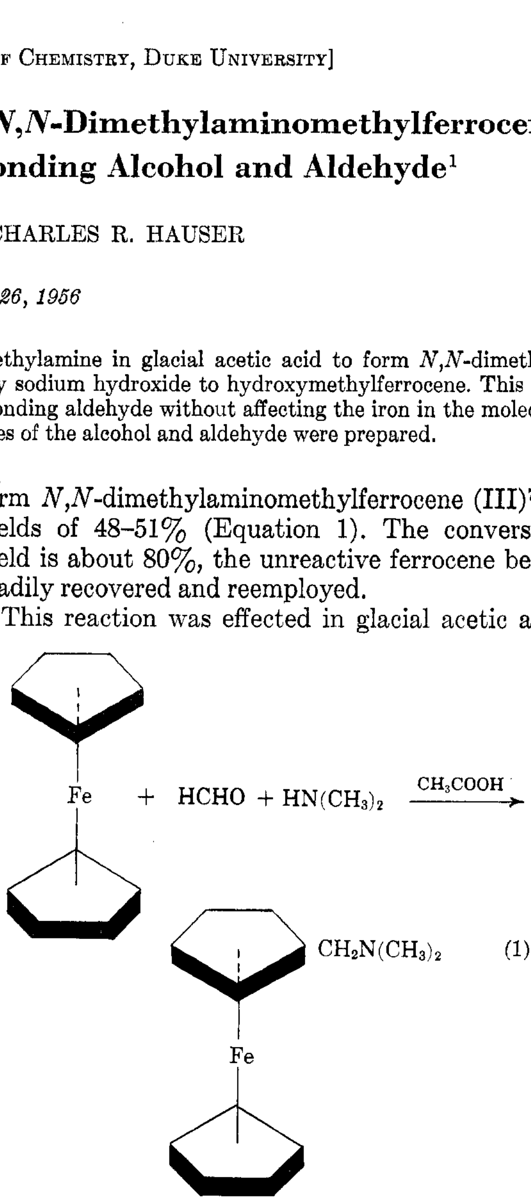
I



II

It has now been found that ferrocene (dicyclopentadienyliron)[6] can be aminomethylated to form *N,N*-dimethylaminomethylferrocene (III)[7] in yields of 48–51% (Equation 1). The conversion yield is about 80%, the unreactive ferrocene being readily recovered and reemployed.

This reaction was effected in glacial acetic acid



(1)

III

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[1] Supported by the Office of Ordnance Research, U. S. Army.

[2] (a) G. F. Hennion, C. C. Price, and V. C. Wolff, Jr., *J. Am. Chem. Soc.*, **77**, 4633 (1955); (b) C. J. Schmidle and R. C. Mansfield, *J. Am. Chem. Soc.*, **77**, 4636 (1955).

[3] H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **70**, 1703 (1948).

[4] See Ref. 2a, and S. L. Meisel, J. J. Dickert, Jr., and H. D. Hartough, *J. Am. Chem. Soc.*, **78**, 4782 (1956).

[5] See Ref. 2a, Ref. 3, and F. F. Blicke, *Org. Reactions*, 1, 303 (1942).

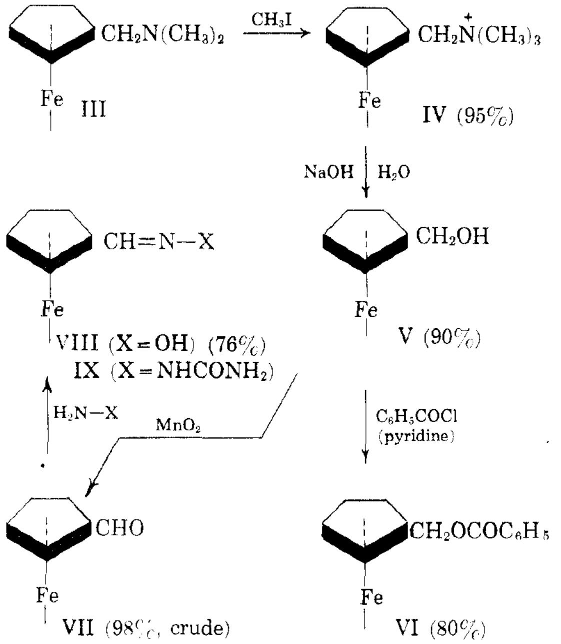
[6] We are indebted to Linde Air Products Co., Tonawanda, N. Y. (Dr. R. L. Pruett) for a generous sample of this compound.

[7] This product was first reported in a communication; C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **21**, 382 (1955). Also in this communication was reported the methiodide of tertiary amine III and a tertiary amine resulting from its rearrangement. The structure of the latter product is being investigated.

with paraformaldehyde and dimethylamine or preferably with paraformaldehyde and *N,N,N',N'-tetramethyldiaminomethane*. The last reagent served as the source of the dimethylamine and half of the formaldehyde. The method is similar to that employed by Schmidle and Mansfield[2b] for the aminomethylation of α-methylstyrene.

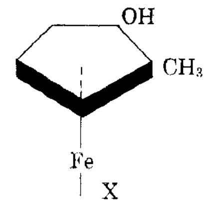
The aminomethylation of ferrocene (Equation 1) furnishes a new route to the synthesis of a number of hitherto unavailable ferrocene derivatives. The preparation of certain of these derivatives[8] is represented by Chart I in which the yields for each step are given in parentheses.

Chart I



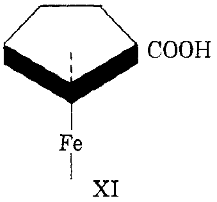
It can be seen from Chart I that tertiary amine III was converted through its methiodide to the corresponding primary alcohol V. This reaction involved presumably the S_N2 type of displacement of trimethylamine which was observed to be formed as a by-product during the course of the reaction. Alcohol V was then converted to its benzoate ester VI and to its corresponding aldehyde VII from which were prepared oxime VIII and semicarbazone IX.

The critical step in this transformation was the S_N2 displacement of trimethylamine from quaternary ion IV by hydroxide ion to form primary alcohol V since the S_N2' type of displacement to give tertiary hydroxy compound X was also possible.[9]

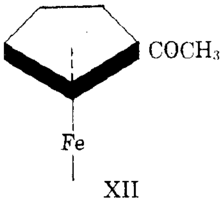


X

That the displacement product was primary alcohol V was demonstrated by its oxidation to aldehyde VII which not only gave appropriate derivatives (Chart I) but also produced a positive Fuchsin-aldehyde test[10] and a strong infrared absorption band for the carbonyl group. Moreover, aldehyde VII underwent the Cannizzaro reaction[10] with alcoholic potassium hydroxide to form the corresponding alcohol and acid, V and XI, respectively. This acid was shown to be identical with an authentic sample of XI prepared from acetylferrocene (XII) by the haloform reaction.



XI



XII

The oxidation of primary alcohol V (Chart I) was effected with a specially prepared manganese dioxide (brown) which has been employed by several workers[11] for the oxidation of benzyl type alcohols to the corresponding aldehydes. Commercial manganese dioxide (black) failed to effect the oxidation, and the alcohol (V) was recovered.

This oxidation of alcohol V to aldehyde VII without affecting the iron in the molecule is of particular interest since the iron in such molecules is known to be sensitive to oxidation. For example, ferrocene has been oxidized with ceric sulfate to form the water-soluble ferricinium ion.[12]

It should be mentioned that oxime VIII was acetylated with acetic anhydride in the cold to form the oxime acetate. An attempt to effect this acetylation at room temperature resulted in a vigorous reaction to produce tar.

EXPERIMENTAL[13]

N,N,N',N'-Tetramethyldiaminomethane. This compound was prepared by a modification of the method of Henry.[14]

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[8] Other derivatives arising through the aminomethylation of ferrocene will be described in later papers.

[9] The nitrile corresponding to hydroxy compound X appears to be produced in the reaction of quaternary ion IV with the cyanide ion although the structure of the product has not yet been definitely established. The analogous reaction of the methiodide of tertiary amine II has been reported to yield not only the corresponding nitrile but also some isomeric nitrile arising from the attack of the cyanide ion on the ring (S_N2' type of reaction); H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **70**, 1857 (1948).

[10] This experiment was carried out by C. E. Cain in this laboratory.

[11] (a) See J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952); (b) R. J. Highet and W. C. Wildman, *J. Am. Chem. Soc.*, **77**, 4399 (1955).

[12] G. Wilkinson, M. Rosenblum, M. C. Whiting, and R. B. Woodward, *J. Am. Chem. Soc.*, **74**, 2125 (1952).

[13] Melting points and boiling points are uncorrected. Analyses are by Galbraith Laboratories, Knoxville, Tenn.

[14] L. Henry, *Bull. Classe Sci. Acad. roy. Belg.*, **26**, 203 (1893).

To an ice-cold, stirred solution of 162 g. (2 mole) of 37% aqueous formaldehyde was added 722 g. (4 moles) of 25% aqueous dimethylamine solution maintaining the temperature below 15°. After stirring 0.5 hr. longer, solid potassium hydroxide was added until two layers separated. The upper layer was removed and dried over solid potassium hydroxide. After filtering, the product was distilled to give 178 g. (87%) of *N,N,N′,N′*-tetramethyldiaminomethane, b.p. 82–84° (reported b.p., about 82°).[14]

Aminomethylation of ferrocene to form tertiary amine III. A mixture of 25.5 g. (0.25 mole) of *N,N,N′,N′*-tetramethyldiaminomethane, 7.9 g. (0.25 mole) of paraformaldehyde and 200 g. (3.3 moles) of glacial acetic acid was heated for a few minutes until solution occurred, and 93 g. (0.5 mole) of ferrocene[6] was then added with stirring. The mixture was stirred and refluxed for 5 hr. All of the ferrocene dissolved within about 1 hr. The solution was cooled slightly, and 500 ml. of water was added with stirring. The resulting mixture was filtered, and the solid was washed with dilute acetic acid, followed by water. This solid consisted largely of unreacted ferrocene which was reemployed in the aminomethylation reaction. The clear filtrate (and washings) was chilled in an ice bath, and made strongly alkaline with 50% sodium hydroxide solution. The resulting mixture was extracted three times with ether, and the combined extract was washed with water. The ethereal solution was dried over magnesium sulfate and, after filtering, the solvent was removed. The residue was distilled *in vacuo* to give 62.2 g. (51%) of *N,N*-dimethylaminomethylferrocene (III) (clear amber), b.p. 91–92° at 0.45 mm., n_D^{25} 1.5893.

Anal.[15] Calcd. for $C_{13}H_{17}FeN$: C, 64.22; H, 7.05; N, 5.76. Found: C, 64.46; H, 6.83; N, 5.85.

The aminomethylation of ferrocene was effected in slightly lower yield (48%) employing free dimethylamine and paraformaldehyde in acetic acid, but the method described above is considered more convenient.

The picrate of tertiary amine III was obtained, after recrystallization from 95% ethanol, as red needles, m.p. 162–163° dec.

Anal. Calcd. for $C_{19}H_{20}FeN_4O_7$: C, 48.32; H, 4.27; N, 11.86; Fe, 11.83. Found: C, 48.22; H, 4.51; N, 11.81; Fe, 11.57.

Methylation of tertiary amine III to form methiodide IV. To a cooled solution of 48.6 g. (0.2 mole) of *N,N*-dimethylaminomethylferrocene (III) in an equal volume of absolute methanol was added dropwise a solution of 45.2 g. (0.3 mole) of methyl iodide in an equal volume of absolute methanol. The clear solution was refluxed for 5 min., and 500 ml. of ether was then added. The resulting precipitate of the quaternary salt (IV) was collected on a funnel, and washed with ether until the washings were colorless. There was obtained 73 g. (95%) of methiodide IV as yellow crystals which decomposed slowly on heating to 220°.

Anal. Calcd. for $C_{14}H_{20}FeIN$: C, 43.66; H, 5.24; N, 3.64; Fe, 14.50. Found: C, 43.50; H, 5.26; N, 3.76; Fe, 14.24.

Reaction of methiodide IV with sodium hydroxide to form alcohol V. To 200 ml. of 1*N* sodium hydroxide solution was added 20.0 g. (0.052 mole) of methiodide IV, and the mixture was refluxed for 2 hr. The evolution of trimethylamine at the top of the condenser was readily detected by its odor and effect on moist litmus paper. After cooling, the oily material was taken up in ether. The ethereal solution (with which was combined an ether extract of the aqueous layer) was washed with water until neutral to litmus, and dried over magnesium sulfate. After filtering, the solvent was removed, and the residual powder recrystallized from hexane to give 10.1 g. (90%) of hydroxymethylferrocene (V) as yellow plates, m.p. 81–82°.

Anal. Calcd. for $C_{11}H_{12}OFe$: C, 61.14; H, 5.60; Fe, 25.85. Found: C, 61.12; H, 5.77; Fe, 25.58.

An infrared absorption spectrum of this compound showed peaks at 3540 cm.$^{-1}$ and at 3450 cm.$^{-1}$ which are characteristic of an alcoholic hydroxyl group. Also bands were observed at 1100 cm.$^{-1}$ and 1000 cm.$^{-1}$ which are characteristic of ferrocene derivatives having substituents in only one of the two cyclopentadienyl rings.[16]

Benzoate of hydroxymethylferrocene (VI). This ester was prepared by treating hydroxymethylferrocene (V) with benzoyl chloride in pyridine.[17] The product was recrystallized from isooctane to give yellow needles, m.p. 130–132°; yield 80%.

Anal. Calcd. for $C_{18}H_{16}O_2Fe$: C, 67.52; H, 5.04; Fe, 17.44. Found: C, 67.52; H, 5.19; Fe, 17.42.

Oxidation of alcohol V to form aldehyde VII. The procedure of Highet and Wildman[11b] for the oxidation of certain benzyl type alcohols with "active" manganese dioxide was adopted. The reagent was prepared as described by Attenburrow and coworkers[11a] except that the precipitate of manganese dioxide, obtained from the alkaline solution, was collected on a funnel and washed with water until the washings were colorless. After drying in an oven at 100–120°, a fine powder was obtained.

To a solution of 10.0 g. of hydroxymethylferrocene (V) in 50 ml. of chloroform was added with cooling 50 g. of the "active" reagent. The resulting slurry became warm. After 8 hr., the mixture was filtered, and the solid washed well with ether. The solvent was removed from the combined filtrate and ethereal washings to leave 9.8 g. (98%) of crude formylferrocene (VII) as a flaky red solid, m.p. 100–115°. After several recrystallizations from 95% ethanol (by chilling) crystals were produced melting at 130–132°, but satisfactory analysis for the aldehyde was not obtained. An infrared spectrum showed strong carbonyl absorption at 1690^{-1}.

The Cannizzaro reaction[10] was realized with 5 g. of the crude aldehyde, 20 g. of potassium hydroxide, 20 ml. of 95% ethanol, and 10 ml. of water. After standing at room temperature for 12 days, the reaction mixture was shaken with ether, and the layers separated. The aqueous layer (after being combined with an aqueous extract of the ether layer) was acidified in the cold, and the resulting mixture extracted twice with ether. The ethereal solution was dried, and the solvent removed *in vacuo* to leave 1.4 g. (27%) of crude carboxylic acid XI which melted at 219–225° dec. after recrystallization from *n*-hexane. A mixed melting point with an authentic sample of acid XI (m.p. 223–227° dec.) was 220–227° dec. The authentic sample was prepared by cleaving acetylferrocene (XII) with potassium hypochlorite.[18] The original ether layer was extracted with saturated sodium bisulfite, washed with water, dried, and worked up to give 1.2 g. (24%) of alcohol V, m.p. 78–80° after recrystallization from *n*-hexane. This melting point was not depressed on admixture with alcohol V (m.p. 81–82°) prepared as described above. A small amount of aldehyde VII was recovered from the bisulfite extract.

Formylferrocene oxime (VIII). To a solution of 15 g. (0.07 mole, assumed pure) of crude formylferrocene (VII) in 100 ml. of 95% ethanol was added a solution of 7.05 g. (0.101 mole) of hydroxylamine hydrochloride in 10 ml. of water. Solid sodium hydroxide (13 g., 0.322 mole) was then added cautiously, and the mixture was refluxed for 2 hr. After cooling, 500 ml. of water was added, and the mixture filtered. The alkaline filtrate was saturated slowly (1 hr.) with carbon dioxide gas, and the resulting precipitate collected on a

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(15) Galbraith laboratories reported an unsuccessful attempt to analyze this compound for iron involving treatment with nitric acid; a violent reaction ensued causing mechanical loss.

(16) (a) See P. L. Pauson, *J. Am. Chem. Soc.*, **76**, 2187 (1954); (b) P. L. Pauson, *Quart. Revs.* (*London*), **9**, 391 (1955).

(17) See R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, New York, N. Y., 1956, p. 212.

(18) See Ref. 16b, p. 392, and *Org. Syntheses*, **Coll. Vol. II**, p. 429 (1943).

funnel, washed with water, and dried. Recrystallization from hexane gave 12.1 g. (76%) of copper colored plates of oxime VIII, m.p. 91–93°.

Anal. Calcd. for $C_{11}H_{11}NOFe$: C, 57.67; H, 4.84; N, 6.12; Fe, 24.38. Found: C, 57.81; H, 4.97; N, 6.19; Fe, 24.29.

A 5-g. sample of oxime VIII was added to 5 ml. of acetic anhydride cooled in an ice bath, and the deep red solution was allowed to stand in the refrigerator overnight.[19] To the cold solution was added 50 ml. of 95% ethanol and a little water to give, on scratching, 4 g. of crystals, m.p. 73–76°. Several recrystallizations from hexane gave orange plates of oxime acetate XIII, m.p. 80–81°.

Anal. Calcd. for $C_{13}H_{13}O_2NFe$: C, 57.59; H, 4.83; N, 5.17; Fe, 20.60. Found: C, 57.89; H, 4.79; N, 5.09; Fe, 20.29.

Formylferrocene semicarbazone (IX). This compound was obtained from a 1-gram sample of crude aldehyde VII, semicarbazide hydrochloride and sodium acetate in ethanol-water solution. Recrystallization of the product from 95% ethanol gave orange flakes, m.p. 217–219° dec.

Anal. Calcd. for $C_{12}H_{13}N_3OFe$: C, 53.16; H, 4.83; N, 15.50; Fe, 20.60. Found: C, 53.38; H, 5.07; N, 15.5; Fe, 20.79.

DURHAM, N. C.

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(19) See C. R. Hauser and C. T. Sullivan, *J. Am. Chem. Soc.*, **55**, 4611 (1933).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MICHIGAN]

Quaternary Hydrazones and Their Rearrangement

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The dimethylhydrazones of several aliphatic and aromatic ketones were prepared, and converted into methiodides which yielded *N,N,N*-trimethylhydrazinium iodide on hydrolysis. The quaternary hydrazones would not undergo a Beckmann type of rearrangement on heating alone, but with sodium ethoxide the Neber variant occurred on compounds having α-hydrogens. The molecular refractions of the dimethylhydrazones and the spectral characteristics of them and their methiodides are reported.

The chemistry of arylhydrazones and to some extent of acylhydrazones has been well developed, but that of alkylhydrazones has been largely neglected, perhaps due in part to the difficult accessibility of alkylhydrazines. The isoelectronic relationship between hydrazones and oximes has led to the speculation that the rearrangements known for oximes should find their parallels with hydrazones. Such rearrangements are characterized by the loss from nitrogen of a species which is the conjugate base of a fairly strong acid, e.g., benzenesulfonate ion. Quaternary hydrazones (I) having three groups on the terminal nitrogen atom might by parallel behavior lose a molecule of tertiary amine, which would satisfy the foregoing characterization

$$R_2C{=}N{-}\overset{+}{N}R_3'X^-$$

I

insofar as the conjugate tertiary ammonium ion is a strong enough acid. The present work was undertaken to elucidate some of the chemistry of alkylhydrazones, with particular attention to the possibility of rearrangements.

Initial attempts to prepare quaternary hydrazones of structure I by reaction of carbonyl compounds with *N,N,N*-trimethylhydrazinium iodide did not succeed. This is not astonishing when one considers the positive charge of the hydrazinium ion and its repulsion for the positive field of the carbonyl carbon atom.

Attention was then turned to N,N-disubstituted hydrazones, which in principle might be further alkylated to quaternary derivatives at either nitrogen. In order to favor terminal alkylation, dimethylhydrazones were chosen, since methyl groups should offer near minimal steric hindrance, and should not decrease the basicity of the terminal nitrogen atom. The preparation of certain dimethylhydrazones from carbonyl compounds and dimethylhydrazine has been reported recently;[2] we were able to repeat and extend the observations reported. Dimethylhydrazine does not react with ketones with the facility shown by aryl- and acyl-hydrazones. This difference is presumably due to the much greater basic strength of dialkylhydrazines, which should reside in the substituted nitrogen atom, a site incapable of hydrazone formation. Furthermore, the simultaneous occurrence of significant concentrations of the free hydrazine and the conjugate acid of the ketone becomes more difficult in proportion to the basic strength of the hydrazine, and it is these two species which appear to react in the rate-determining step of hydrazone formation.[3] We were successful in overcoming the inherent difficulties by using excess anhydrous dimethylhydrazine, at reflux temperatures or in sealed tubes, as the situation warranted. An alternative route to

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(1) From the doctoral thesis of E. E. Most, Jr., whose present address is E. I. du Pont de Nemours and Co., Kinston, Va.

(2) D. Todd, *J. Am. Chem. Soc.* **71**, 1353 (1949).

(3) J. B. Conant and P. D. Bartlett, *J. Am. Chem. Soc.*, **54**, 2881 (1932); *cf.* E. R. Alexander, *Principles of Ionic Organic Reactions*, John Wiley and Sons, Inc., New York, 1950, pp. 154–165.