

Advances in

HETEROCYCLIC CHEMISTRY

Edited by

A. R. KATRITZKY

A. J. BOULTON

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CHEMISTRY**

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A. J. BOULTON

*School of Chemical Sciences
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Preface

Volume 13 of this serial publication comprises six chapters of which four deal with general accounts of compound classes: 1-azirines (F. W. Fowler), phenanthridines (B. R. T. Keene and P. Tissington), tri-thiapentalenes (N. Lozac'h), and heterocyclic ferrocenes (F. D. Popp and E. B. Moynahan). The other two chapters are concerned with particular aspects of the chemistry of groups of heterocycles: the tautomerism of purines (B. Pullman and A. Pullman) and quantitative aspects of the electrophilic substitution reactions of five-membered rings (G. Marino).

A. R. KATRITZKY
A. J. BOULTON

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Heterocyclic Ferrocenes

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I. Introduction

Since the discovery of dicyclopentadienyliron (ferrocene) in 1951^{1, 2} an immense body of literature has appeared concerning the chemistry of ferrocenes and related compounds. Although a large number of reviews³ have appeared, they have given only brief treatment to ferrocenes containing heterocyclic systems. It is the purpose of this review to report on those ferrocenes which contain heterocyclic systems either fused to the ferrocene or as a substituent on the ferrocene.

The literature has been surveyed through mid-1970 and it is believed that all papers dealing specifically with heterocyclic ferrocenes, as well as most papers where such compounds were only incidental to the main theme of the paper, are included in this review.

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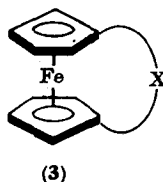
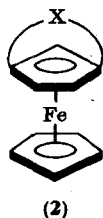
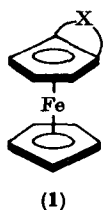
¹ T. J. Kealy and P. L. Pauson, *Nature (London)* **168**, 1039 (1951).

² S. A. Miller, J. A. Tebboth, and J. F. Tremaine, *J. Chem. Soc.* 632 (1952).

³ See D. E. Bublitz and K. L. Rinehart, Jr., *Org. React.* **17**, 1 (1969) for a recent review and references to 41 other reviews.

II. Ferrocenes Containing a Heterocyclic Ring Fused to the Ferrocene

Although ferrocene is theoretically capable of forming three types of cyclized structures (1, 2, and 3), only examples of 1 and 3 have been reported, with a heteroatom in the chain connecting the 1 and 2 carbons of one five-membered ring and in the bridge between the 1- and 1'-positions of ferrocene. The number of compounds of these two types are relatively few as compared with those in which ferrocene is a substituent on the heterocyclic compound (Section III). Relatively little has been reported regarding the chemistry of these compounds, despite the obvious potential of comparing the physical and chemical properties of ferroceno heterocyclic compounds (1) with the corresponding benzo compounds.



A. FERROCENO HETEROCYCLIC COMPOUNDS

1. Nitrogen-Containing Ferroceno Heterocyclic Compounds

The first reported ferroceno heterocyclic compound of the type 1 was *N*-methyltetrahydropyridoferrocene (4). This compound was obtained from an anomalous Leuckart-Eschweiler-Clark reaction of 2-aminomethylferrocene (5; R = H), formaldehyde, and formic acid,⁴ although the structure 4 was not immediately recognized for this compound.⁵⁻⁸ The heterocyclic compound 4 can be used as an entry to 1,2-disubstituted ferrocenes since on reaction with potassium amide in liquid ammonia⁷ or with potassium hydroxide in methanol⁹ its

⁴ D. Lednicer, J. K. Lindsay, and C. R. Hauser, *J. Org. Chem.* **23**, 653 (1958).

⁵ J. M. Osgerby and P. L. Pauson, *Chem. Ind. (London)* 196 (1958).

⁶ J. M. Osgerby and P. L. Pauson, *Chem. Ind. (London)* 1144 (1958).

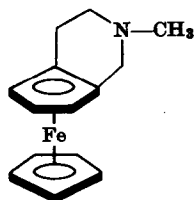
⁷ D. Lednicer and C. R. Hauser, *J. Org. Chem.* **24**, 43 (1959).

⁸ J. M. Osgerby and P. L. Pauson, *J. Chem. Soc.* 4600 (1961).

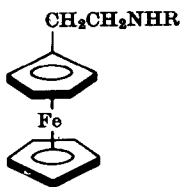
⁹ K. Schlögl, M. Fried, and H. Falk, *Monatsh. Chem.* **95**, 576 (1964).

methiodide gives 6. Reaction of 5 ($R = CH_3$) with formaldehyde gave 7, which could be converted into 4 by action of phosphoric acid.^{6, 8}

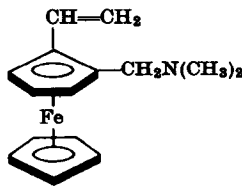
Bischler-Napieralski ring closure of 5 ($R = CH_3$) with phosphorus oxychloride^{6, 8, 9} and of 5 ($R = COCH_3$) with phosphorus oxychloride^{6, 8} or polyphosphate ester¹⁰ gave 8 ($R = H$ and $R = CH_3$, respectively). Reduction of 8 ($R = H$) with lithium aluminum hydride



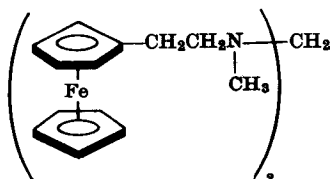
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(5)



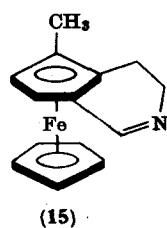
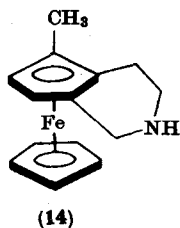
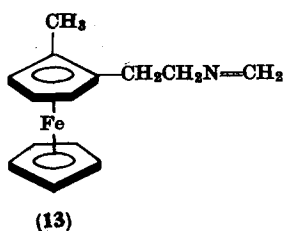
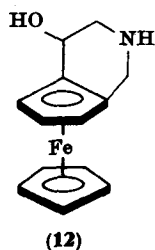
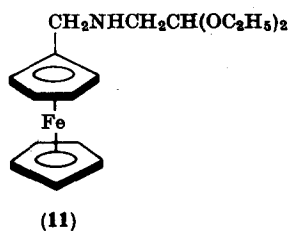
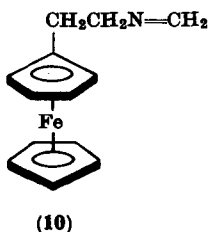
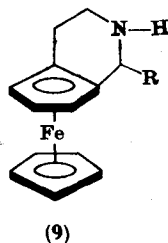
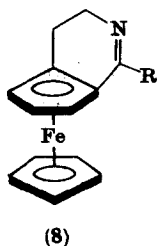
(6)



(7)

followed by methylation with dimethyl sulfate gave 4.^{6, 8} Reduction of 8 ($R = CH_3$) was also carried out⁸ to give 9 ($R = CH_3$) which could not be dehydrogenated to an isoquinoline analog under a wide range of conditions.^{8, 10} Although 9 ($R = H$) was not characterized in the conversion of 8 ($R = H$) to 4, it was isolated by reduction of 8 ($R = H$) with lithium aluminum hydride or catalytically.⁹ This same compound (9; $R = H$) was also obtained by treatment of 10 with hydrochloric acid⁹ or by treatment of 11 with hydrochloric acid followed by hydrogenation.¹⁰ If the hydrogenation step was omitted in this latter procedure, 12 could be isolated as its hydrochloride salt.¹⁰ An attempt to cyclize, with hydrochloric acid, the homolog of 10 containing one less carbon atom led to polymer formation.⁹ The amine 9 ($R = H$) has been resolved through crystallization of its (-)-*o,o'*-dinitrodiphenic acid salt.

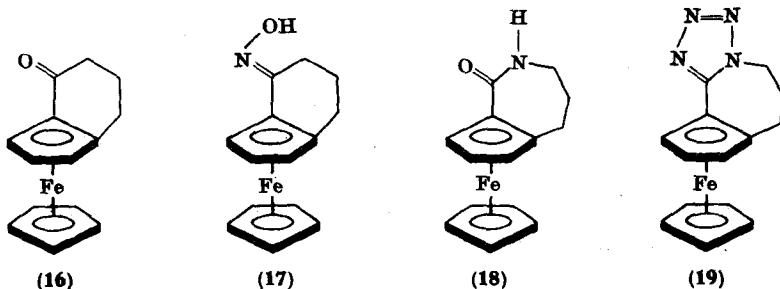
¹⁰ F. D. Popp and E. B. Moynahan, unpublished results.



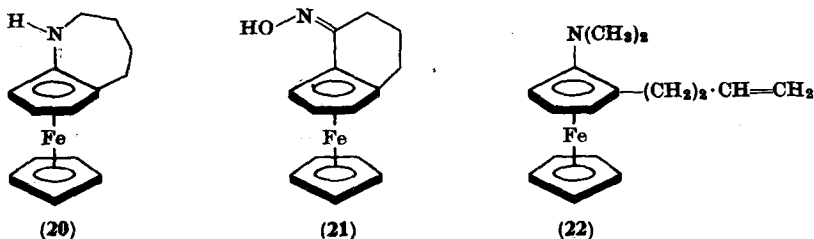
The 1,2-disubstituted ferrocene (13) on treatment with hydrochloric acid gives 14 which can be oxidized with manganese dioxide to give 15.⁹

The Schmidt reaction of 1,2-(α -ketotetramethylene)ferrocene (16) with hydrazoic acid and sulfuric acid in benzene⁹ or the Beckmann

rearrangement of 17 with *p*-toluenesulfonyl chloride¹¹ gave the lactam (18). In the case of the Schmidt reaction the optically active (+)-ketone was used and gave (-)-18 as well as the (-)-tetrazole (19).⁹ Reduction of (-)-19 with lithium aluminum hydride gave the (-)-homolog of 9 ($R = H$), which was oxidized with manganese dioxide to give the (-)-homolog of 8 ($R = H$).⁹



Treatment of the oxime (17) with lithium aluminum hydride-aluminum chloride led to a rearrangement of the ferrocene residue to give 20.¹¹ The oxime (21) was unchanged under these conditions. Treatment of the quaternary methiodide of 20 with base led to the ring-opened product (22).

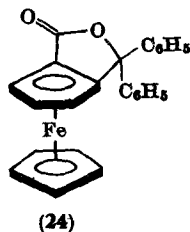
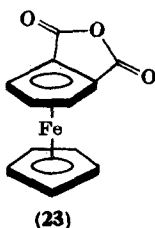


2. Oxygen-Containing Ferrocene Heterocyclic Compounds

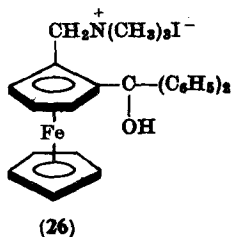
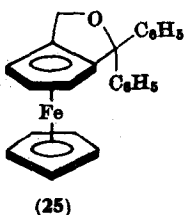
The activity in the field of ferrocene heterocyclic compounds of the type 1 has been even less in the case of oxygen-containing compounds than it was with nitrogen-containing compounds. As might be anticipated, the first two examples of this class of compounds were an anhydride and a lactone. Thus treatment of ferrocene-1,2-dicarboxylic

¹¹ K. Schlögl and H. Mechtler, *Monatsh. Chem.* **97**, 150 (1966).

acid with *N,N'*-dicyclohexylcarbodiimide gave 23¹² and the action of heat or acid on the appropriate hydroxy acid gave 24.¹³



The cyclic ether (25) has been prepared via the cyclization of 26 in monoglyme with potassium amide.^{14, 15} The magnetic nonequivalence of the methylene group protons in 25 have been compared with other 1,2-disubstituted ferrocenes.¹⁶



3. Miscellaneous Ferrocene Heterocyclic Compounds

Treatment of the acid chloride of *S*-ferrocenylmethylthioglycolic acid with stannic chloride in methylene chloride at -70° gave 1,2-(2-thia-4-oxotetramethylene)ferrocene (27).¹⁷ Reaction of 27 with Raney nickel led to ring opening and gave a mixture of 1-methyl-2-ethyl-

¹² J. H. Richards and T. J. Curphey, *Chem. Ind. (London)* 1456 (1956).

¹³ R. A. Benkeser, W. P. Fitzgerald, and M. S. Melzer, *J. Org. Chem.* **26**, 2569 (1961).

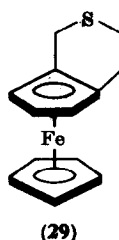
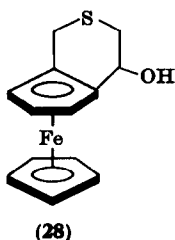
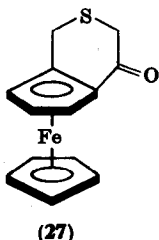
¹⁴ D. W. Slocum, B. W. Rockett, and C. R. Hauser, *Chem. Ind. (London)* 1831 (1964).

¹⁵ D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Amer. Chem. Soc.* **87**, 1241 (1965).

¹⁶ P. Smith, J. J. McLeskey, III, and D. W. Slocum, *J. Org. Chem.* **30**, 4356 (1965).

¹⁷ A. N. Nesmeyanov, E. G. Perevalova, L. I. Leonteva, and Yu. A. Ustynyuk, *Izv. Akad. Nauk. SSSR, Ser. Khim.* 1882 (1965); *Chem. Abstr.* **64**, 2123 (1966).

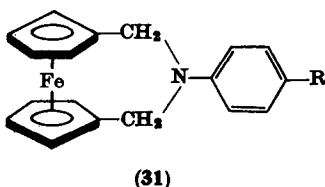
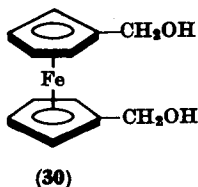
ferrocene and 1-methyl-2-acetylferrocene. Reduction of **27** with lithium aluminum hydride gave the corresponding alcohol (**28**), whereas use of aluminum chloride with the lithium aluminum hydride gave 30% methylferrocene, 5% **28**, and 40% 1,2-(2-thiatetramethylene)ferrocene (**29**).¹⁷



B. BRIDGED HETEROCYCLIC COMPOUNDS

1. Compounds with Nitrogen in the Bridge

Reaction of the heteroannular diol (**30**) with phenylisocyanate or *p*-methoxyphenylisocyanate at room temperature gave the expected urethans, but use of these isocyanates at elevated temperature or use of *p*-nitrophenylisocyanate at room or elevated temperature gave the bridged amine (**31**; R = H, OCH₃, and NO₂).¹⁸ The NMR spectrum of **31** shows a triplet for the ferrocene ring protons.¹⁹ This triplet is attributed to the direct inductive influence on the α -ring proton of the bridge nitrogen atom.

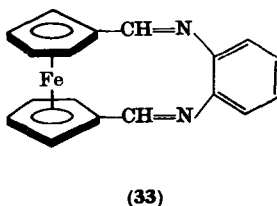
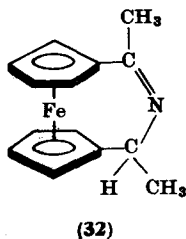


Reduction of the monooxime of 1,1'-diacetylferrocene with lithium aluminum hydride-aluminum chloride gave a mixture of products which apparently included the bridged amine (**32**).¹¹ A compound,

¹⁸ H. J. Lorkowski and P. Kieselack, *Chem. Ber.* **99**, 3619 (1966).

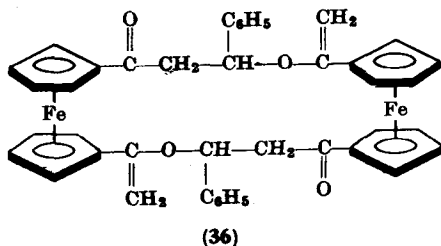
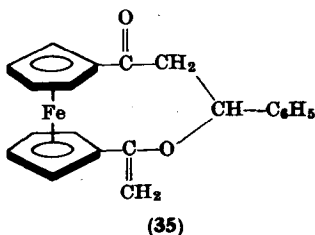
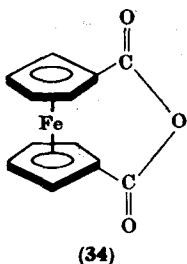
¹⁹ H. J. Lorkowski, G. Engelhart, P. Kieselack, and H. Jancke, *J. Organometal. Chem.* **7**, 523 (1967).

whose analysis was in approximate agreement with the bridged structure (33), was obtained from the reaction of *o*-phenylenediamine and ferrocene-1,1'-dicarboxaldehyde.²⁰



2. Compounds with Oxygen in the Bridge

Just as homoannular ferrocenedicarboxylic acid leads to a cyclic anhydride (23), so does the heteroannular ferrocenedicarboxylic acid. Thus treatment of the dichloride of ferrocene-1,1'-dicarboxylic acid with water in chloroform-pyridine gave the anhydride (34).²¹ Treatment of 34 with ammonium hydroxide led to ring opening and formation of the diamide and the monoamide-monoacid.²¹

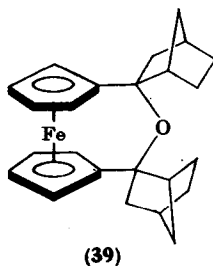
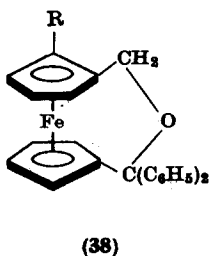
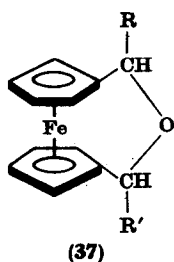


²⁰ J. M. Osgerby and P. L. Pauson, *J. Chem. Soc.* 4604 (1961).

²¹ A. N. Nesmeyanov and O. A. Reutov, *Dokl. Akad. Nauk SSSR* 120, 1267 (1958); *Chem. Abstr.* 53, 1292 (1959).

Reaction of 1,1'-diacetylferrocene and benzaldehyde with 5% aqueous-ethanolic sodium hydroxide gave the expected dibenzal derivative and a yellow compound believed to be 35 or 36.²²

The remaining heterocyclic compounds with oxygen in the bridge are ethers of the types 37 and 38. The parent compound (37; $R = R' = H$) has been obtained by treatment of 1,1'-di(hydroxymethyl)ferrocene with *p*-toluenesulfonyl chloride in refluxing benzene²³ or with 10% hydrochloric acid in ether.²⁴ The ring protons appear as a singlet in the NMR spectrum of 37 ($R = R' = H$).²³ In a similar manner other diols have been dehydrated with *p*-toluenesulfonyl chloride, acid alumina, dilute hydrochloric acid, dilute acetic acid, and silica to give 37 ($R = R' = CH_3$)²⁵⁻³²; $R = R' = C_6H_5$)²⁵⁻²⁷.



²² T. A. Mashburn, Jr., C. E. Cain, and C. R. Hauser, *J. Org. Chem.* **25**, 1982 (1960).

²³ K. L. Rinehart, Jr., A. K. Frerichs, P. A. Kittle, L. F. Westman, D. H. Gustafson, R. L. Pruett, and J. E. McMahon, *J. Amer. Chem. Soc.* **82**, 4111 (1960).

²⁴ A. N. Nesmeyanov, S. S. Churanov, Yu. A. Ustynyuk, and E. G. Perevalova, *Izv. Akad. Nauk SSSR, Ser. Khim.* 1648 (1966); *Chem. Abstr.* **66**, 65613j (1967).

²⁵ P. L. Pauson, M. A. Sandhu, and W. E. Watts, *J. Chem. Soc. C* 251 (1966).

²⁶ K. Schlögl and A. Mohar, *Naturwissenschaften* **48**, 376 (1961).

²⁷ K. Schlögl and A. Mohar, *Monatsh. Chem.* **92**, 219 (1961).

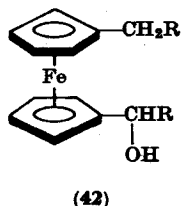
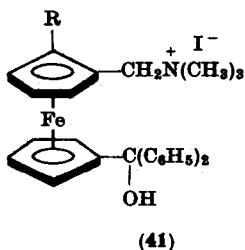
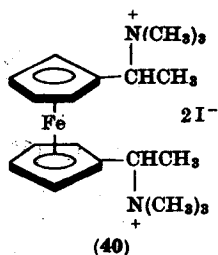
²⁸ T. A. Mashburn, Jr. and C. R. Hauser, *J. Org. Chem.* **26**, 1671 (1961).

²⁹ E. C. Winslow and E. W. Brewster, *J. Org. Chem.* **26**, 2982 (1961).

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³¹⁻³⁵; $R = R' = n\text{-C}_5\text{H}_{11}$ ^{32, 33}; $R = \text{CH}_3$, $R' = \text{C}_6\text{H}_5$ ³²; $R = \text{CH}_3$, $R' = \text{C}_2\text{H}_5$ ^{32, 33}; and $R = \text{CH}_3$, $R' = \text{H}$ ³⁶). In a similar manner the appropriate diol with *p*-toluenesulfonyl chloride gave **39**.³⁷ The cyclic ether (**37**; $R = R' = \text{CH}_3$) has also been obtained^{25, 38} by hydrolysis of the dimethiodide (**40**). The methiodide (**41**) has been cyclized to the ether (**38**; $R = \text{H}$) by action of sodamide in dimethylformamide.³⁹ With **41** [$R = \text{C}(\text{C}_6\text{H}_5)_2\text{OH}$] the ether [**38**; $R = \text{C}(\text{C}_6\text{H}_5)_2\text{OH}$] was obtained³⁹ rather than an ether of the type **25**.

The ethers (**37**; $R = R' = \text{CH}_3$ or C_6H_5) can be converted into low yields of diols by prolonged treatment with acidic alumina.³¹ Treatment of **37** ($R = R' = \text{H}$ or CH_3) with lithium aluminum hydride-aluminum chloride gave 1,1'-dimethylferrocene and 1,1'-diethylferrocene, respectively.⁴⁰ Action of lithium in tetrahydrofuran on **37** ($R = R' = \text{H}$)²⁴ or ($R = R' = \text{CH}_3$ or C_6H_5)³⁴ led after hydrolysis to ring-opened products of the type **42** ($R = \text{H}$, CH_3 , and C_6H_5 , respectively). In the case of **37** ($R = R' = \text{C}_6\text{H}_5$) some 1,1'-dibenzylferrocene and other products were obtained in addition to **42** ($R = \text{C}_6\text{H}_5$).³⁴ The visible and ultraviolet absorption spectra of **37** and **38** have been reported⁴¹ and compared with other ferrocene derivatives.

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