

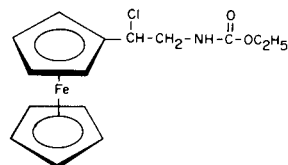
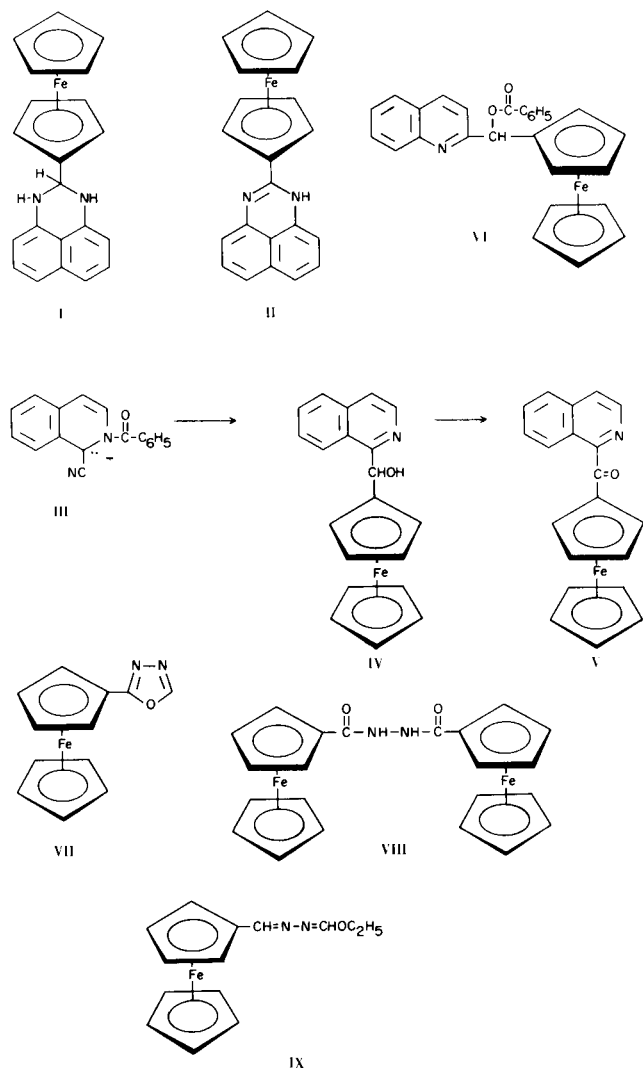
Ferrocene Studies. VI. Some Heterocyclic Derivatives of Ferrocene (1)

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Despite the large volume of work reported on ferrocene and its derivatives, relatively little has appeared concerning heterocyclic derivatives of ferrocene. In connection with work in progress in this laboratory it was necessary to prepare a variety of such compounds and this paper describes that work.

Ferrocenecarboxaldehyde provides an ideal starting point for such work and the compounds shown in Table I were prepared by the condensation of this aldehyde with heterocyclic amines and hydrazines. Condensation of



ferrocenecarboxaldehyde with 1,8-diaminonaphthalene gave the 2,3-dihydro-1H-perimidine (I) which was dehydrogenated to II with palladium on carbon. Compound II could also be obtained directly by carrying out the condensation in the presence of palladium on charcoal.

The condensation of ferrocenecarboxaldehyde with the anion of the isoquinoline Reissert Compound (2) (III) led to the isolation of the carbinol form (IV). This carbinol was oxidized to V with manganese dioxide. Use of the anion of the quinoline Reissert Compound gave rise to VI.

The reaction of ferrocenecarboxyhydrazide with triethylorthoformate gave three products, the principal one being 2-ferrocenyl-1,3,4-oxadiazole (VII). The two remaining products appear to be VIII and IX. The spectral data on these three products is included in the Experimental Section.

Ethyl N-(2-chloro-2-ferrocenylethyl)carbamate (X) was synthesized by the method of Foglia and Swern (3) from vinylferrocene and dichlorourethane. Attempts to convert X into heterocyclic compounds (3) did not lead to any useful products.

EXPERIMENTAL (4)

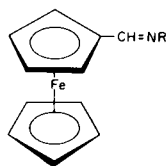
Condensations with Ferrocenecarboxaldehyde.

Equimolar quantities of ferrocenecarboxaldehyde and the amines and related compounds listed in Table I were dissolved in minimum of absolute ethanol and heated on the steam bath for 15 to 30 minutes. After cooling the compounds listed in Table I were obtained by filtration.

2-Ferrocenyl-2,3-dihydro-1H-Perimidine (I).

A mixture of 15.0 g. (0.0705 mole) of ferrocenecarboxaldehyde, 11.14 g. (0.0705 mole) of 1,8-diaminonaphthalene and a small amount of *p*-toluenesulfonic acid in 200 ml. of benzene was refluxed in a Dean-Stark apparatus for 12 hours and filtered hot. Cooling and filtration gave 20.52 g. (83%) of I, m.p. 182-183° from benzene; IR (potassium bromide), 3380, 1600, 1110, 1005

TABLE I



RNH ₂	M.p. °C (ab)	Yield %	Formula	Analyses		I.R. (c) (potassium bromide) Cm ⁻¹
				Calcd.	Found	
				C	H	
3-Aminocarbazole (d)	192-193 (e)	64	C ₂₃ H ₁₈ FeN ₂	73.03 72.97	4.80 4.80	3230, 1640(s), 1630, 1590 (s), 1110, 1010
3(2-Aminoethyl)indole (d)	150-152	75	C ₂₁ H ₂₀ FeN ₂	70.80 70.85	5.66 5.68	3040, 2940, 1645, 1615(s), 1110, 1000
2-Hydrazino-4-hydroxy-6-methylpyrimidine (f)	208-210	81	C ₁₆ H ₁₆ FeN ₄ O	57.16 57.24	4.80 4.84	3350(w), 3185(s), 3090(w), 2800, 1670, 1610, 1110, 1005
Indole-3-acetic acid hydrazide	231-233	99	C ₂₁ H ₁₉ FeN ₃ O	65.46 65.60	4.97 5.16	3340, 3230, 3075, 1670, 1650, 1610, 1510, 1005
2-Hydrazinopyridine	170-172 (g)	63	C ₁₆ H ₁₅ FeN ₃	62.97 63.05	4.95 5.05	3200, 3100, 2980, 1605, 1100, 1005
2-Hydrazinoquinoline	97-98 (h)	50	C ₂₀ H ₁₇ FeN ₃ (i)	67.62 67.61	4.82 4.93	3450(w,b), 3240(w), 3100(w,b), 1620, 1580(s), 1115, 1005
Isonicotinic acid hydrazide (j)	210-211	93	C ₁₇ H ₁₅ FeN ₃ O	61.28 61.03	4.54 4.46	3400, 3150, 3100, 1675, 1610, 1115, 1005,

(a) Recrystallized from ethanol unless otherwise noted. (b) M.p. with decomposition and generally with considerable darkening below the m.p. (c) s = shoulder, w = weak, b = broad. (d) The preparation of these compounds was supported by a research grant (CA 10345) from the National Cancer Institute, U.S.P.H.S. (e) Compound not recrystallized. (f) Forms a very stable hydrate, C₁₆H₁₆FeN₄O·H₂O, Calcd.: C, 54.25; H, 5.12; Found: C, 54.21; H, 4.99, and vigorous drying is required (48 hours at 100° *in vacuo*) to obtain the unhydrated form. (g) Recrystallized from benzene. (h) Recrystallized from heptane after chromatography. (i) Hydrochloride salt prepared, m.p. 216-217 (chloroform-heptane); Calcd.: Cl, 9.05; Found: Cl, 9.17. (j) Few drops of acetic acid added to reaction mixture and reaction run at 50° for 3 hours.

cm⁻¹; NMR (DMSO-d₆): 4.48 (5), 4.32 (2), 4.57 (2) (9 Fc); 5.64 (1) (CH); 6.58 (2) (NH); 6.91-7.75 (6) (Ar) δ.

Anal. Calcd. for C₂₁H₁₈FeN₂: C, 71.20; H, 5.12; N, 7.90. Found: C, 71.25; H, 5.03; N, 7.84.

2-Ferrocenyl-1H-perimidine (II).

A mixture of 1.0 g. (0.0047 mole) of ferrocenecarboxaldehyde and 0.743 g. (0.0047 mole) of 1,8-diaminonaphthalene in 50 ml. of xylene with 0.0743 g. of 10% palladium-charcoal was refluxed for 12 hours. The mixture was filtered and the residue extracted with hot DMF. Addition of water to the DMF gave II, m.p. 252-255° from benzene; IR (potassium bromide), 3400, 1630, 1110, 1005

cm⁻¹; NMR (DMSO-d₆), 4.43 (5), 5.28 (2), 4.66 (2) (9 Fc); 1.07 (1) (NH); 6.92-7.75 (6) (Ar).

Anal. Calcd. for C₂₁H₁₆FeN₂: C, 71.60; H, 4.58; N, 7.95. Found: C, 71.19; N, 4.92; N, 7.85.

Treatment of 2.0 g. of I with 0.20 g. of 10% palladium-charcoal in 50 ml. of xylene by a similar procedure also gave II. Ferrocenyl 1-Isoquinolylicarbinol (IV).

To 14.64 g. (0.0564 mole) of 2-benzoyl-1,2-dihydroisoquin-aldonitrile in a mixture of 560 ml. of anhydrous ethyl ether and 110 ml. of anhydrous dioxane under nitrogen at -30° was added

28.0 ml. of 2.5 *N* *n*-butyllithium in hexane. Immediately following this addition, 12.0 g. of ferrocenecarboxaldehyde in 80 ml. of a 1:1 mixture of ether-dioxane was added over 10 minutes at -30° . The reaction was allowed to warm slowly to room temperature over 1 hour and 100 ml. of water was added. Extraction with ether followed by concentration of the washed (water) and dried (magnesium sulfate) extract gave a solid which was chromatographed on grade II alumina with benzene. Recrystallization of this material gave 16.5 g. (85%) of IV, m.p. $160-162^{\circ}$ from benzene; IR (potassium bromide), 3300, 1625, 1110, 1010 cm^{-1} .

Anal. Calcd. for $\text{C}_{20}\text{H}_{15}\text{FeNO}$: C, 69.99; H, 4.99; N, 4.08. Found: C, 70.07; H, 4.92; N, 3.96.

Ferrocenyl 1-Isoquinolyl-ketone.

To 14.0 g. (0.0408 mole) of IV in 250 ml. of chloroform was added 70.0 g. of activated manganese dioxide and the mixture was stirred for 12 hours at room temperature and filtered. The residue was washed with chloroform and the combined washings and filtrate were concentrated *in vacuo* to give a quantitative yield of V, m.p. $113-115^{\circ}$ from ethanol-water; IR (potassium bromide), 1635, 1115, 1005 cm^{-1} .

Anal. Calcd. for $\text{C}_{20}\text{H}_{15}\text{FeNO}$: C, 70.40; H, 4.43; N, 4.11. Found: C, 70.51; H, 4.56; N, 4.13.

Ferrocenyl 2-Quinolylcarbonylbenzoate (VI).

Reaction of the anion of 1-benzoyl-1,2-dihydroquinolone with ferrocenecarboxaldehyde as described above for the preparation of IV gave, without the chromatography step, a quantitative yield of VI, m.p. with slow decomposition from $92-125^{\circ}$ (from ether); IR (potassium bromide), 1715, 1105, 1005 cm^{-1} .

Anal. Calcd. for $\text{C}_{27}\text{H}_{21}\text{FeNO}_2$: C, 72.50; H, 4.73; N, 3.13. Found: C, 72.33; H, 4.84; N, 3.08.

Reaction of Ferrocenecarboxyhydrazide with Triethylorthoformate.

A mixture of 10.0 g. of ferrocenecarboxyhydrazide and 80 ml. of freshly distilled triethylorthoformate were heated to reflux under a nitrogen atmosphere for 12 hours and the excess triethylorthoformate was removed *in vacuo*. This residue was chromatographed on grade II alumina. The use of benzene-heptane gave 4.5 g. (43%) of 2-ferrocenyl-1,3,4-oxadiazole (VII), m.p. $120-122^{\circ}$ from heptane; IR (potassium bromide), 1595, 1520, 1110, 1095, 1005, 950 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{FeN}_2\text{O}$: C, 56.73; H, 3.97; N, 11.03. Found: C, 56.75; H, 4.13; N, 10.88.

Elution with benzene-chloroform and recrystallization from benzene gave 0.5 g. of IX, m.p. $164-165^{\circ}$; IR (potassium bromide), 3185, 1630, 1480, 1270, 1175, 1110, 1035, 1025, 1005, 825 cm^{-1} .

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{FeN}_2\text{O}$: C, 59.18; H, 5.68; N, 9.86; Fe, 19.66. Found: C, 59.21; H, 5.73; N, 9.85; Fe, 19.73.

Elution with chloroform and recrystallization from benzene gave a small amount of VIII, m.p. $275-276^{\circ}$; IR (potassium bromide), 3400, 3200, 1615, 1600, 1500, 1280, 1110, 1005 cm^{-1} .

Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{Fe}_2\text{N}_2\text{O}_2$: C, 57.93; H, 4.42; N, 6.14; Fe, 24.49. Found: C, 57.78; H, 4.51; N, 6.12; Fe, 24.39.

Ethyl *N*-(2-Chloro-2-ferrocenylethyl)carbamate (X).

To 10.0 g. (0.047 mole) of vinylferrocene in 150 ml. of anhydrous benzene which had been purged with deoxygenated, anhydrous nitrogen for 30 minutes was added dropwise at $5-10^{\circ}$ under nitrogen 7.45 g. (0.047 mole) of *N,N*-dichlorourethane. After the addition was complete the mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. The reaction mixture was cooled and 50 ml. of a 20% solution of sodium bisulfite was added. The organic layer was removed and the aqueous layer was extracted with ether. The combined organic materials were washed (20% sodium chloride solution), dried (sodium sulfate), and concentrated *in vacuo*. Chromatography of the residue on grade II alumina with benzene gave 8.17 g. (52%) of X, m.p. $79-80^{\circ}$ from cyclohexane; IR (potassium bromide), 3335, 3090, 2985, 2950, 1685, 1110, 1005 cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{ClFeNO}_2$: C, 53.68; H, 5.45; N, 4.21. Found: C, 54.04; H, 5.35; N, 4.16.

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