ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORIES, UNIVERSITY OF NORTH CAROLINA]

Amides of Ferrocenemonocarboxylic Acid. A Convenient Method for Preparing Ferrocenemonocarboxylic Acid and Heteroannular Substituted Derivatives[1]

BY WILLIAM F. LITTLE AND ROBERT EISENTHAL[2]

RECEIVED JULY 7, 1959

Both the unsubstituted amide and the N,N-diphenylamide of ferrocenemonocarboxylic acid have been prepared directly with ferrocene and carbamyl chloride and N,N-diphenylcarbamyl chloride, respectively, *via* a Friedel–Crafts type reaction. Using two equivalents of the diphenylcarbamyl chloride per mole of ferrocene, only a small amount of the heteroannular bis-diphenylcarboxamide was obtained. Both the unsubstituted amide and the diphenylcarboxamide were hydrolyzed to ferrocenemonocarboxylic acid, and both underwent Friedel–Crafts acylations to give heteroannular acylferrocene monocarboxamides. The acyl derivatives of N,N-diphenylferrocene carboxamide underwent hydrolysis to the corresponding acylferrocenemonocarboxylic acids.

Ferrocenemonocarboxylic acid has been prepared by several methods, all of which suffer from some disadvantages or limitations if applied to the preparation of substituted acids. Monoacetylferrocene can be oxidized with hypoiodite,[3] I_2 in pyridine[4] and NaClO.[5] These methods do not give outstanding yields and could cause difficulty in the preparation of substituted ferrocenemonocarboxylic acids when functional groups other than the acyl group are present in the molecule and might be subject to oxidation. Metallation of ferrocene with butyllithium, with subsequent carbonation, is complicated in that from the lithiation both mono- and dilithioferrocene are produced, regardless of the proportion of the reactants, and carbonation thus yields a mixture of the mono- and dicarboxylic acids,[6–8] though they can be separated readily by ether extraction.[8] Further, for preparation of substituted acids by this method, other functional groups present on the ferrocene nucleus might be attacked by the organometallic reagent.

The present methods for preparing ferrocenemonocarboxylic acid were developed in a search for a convenient method for introducing but one carboxyl group into the ferrocene nucleus, under conditions that are neither oxidative nor reductive, and a method that would lend itself to the preparation of substituted ferrocenemonocarboxylic acids. This has been accomplished by introducing the carboxyl group in the form of the N,N-diphenylamide into the nucleus with a Friedel–Crafts reaction between N,N-diphenylcarbamyl chloride and ferrocene with $AlCl_3$. This method for introducing the carboxyl group was used previously on *o*-xylene by Morgan and Coulson[9] and on benzene by Lellman and Bonhoffer.[10] From this reaction, diphenylcarbamylferrocene (I) (ferrocene-N,N-diphenylcarboxamide) was produced in good yield and was hydrolyzed readily to ferrocenemonocarboxylic acid (III) in alkaline ethanol. Isolation and purification of the substituted amide was not necessary for the preparation of ferrocenemonocarboxylic acid. Using a molar ratio of diphenylcarbamyl chloride and ferrocene, only the monoamide was obtained; with a 2:1 molar ratio of diphenylcarbamyl chloride to ferrocene, a small amount of the bis-diphenylcarbamylferrocene (II) was obtained, though the major product was the monoamide. The difficulty of introducing a second diphenylcarbamyl group into the ferrocene nucleus is interpreted in terms of the relative weakness of the diphenylcarbamyl chloride as a Friedel–Crafts reagent rather than to an overbearing deactivation of the nucleus by the first diphenylcarbamyl group introduced. This is substantiated by the observed failure of acetylferrocene to react with diphenylcarbamyl chloride and $AlCl_3$ (acetylferrocene is readily substituted by a second acetyl group under these conditions with acetyl chloride), while diphenylcarbamylferrocene is easily converted to 1-acetyl-1′-diphenylcarbamylferrocene (IVa).

Acylation of diphenylcarbamylferrocene, with subsequent by alkaline hydrolysis, provides a convenient route to heteroannular substituted ferrocenemonocarboxylic acids. 1′-Acetylferrocene-1-carboxylic acid (Va) has been obtained from IVa. Benzoylation of diphenylcarbamylferrocene in a similar manner gave the heteroannular benzoyldiphenylcarbamylferrocene (IVb), which was easily hydrolyzed to 1′-benzoylferrocene-1-carboxylic acid (Vb).

Ferrocene monocarboxamide (VI) can be prepared directly in a one-step procedure by this same reaction using carbamyl chloride, produced by pyrolysis of cyanuric acid in HCl,[11] in the place of diphenylcarbamyl chloride. The amide of ferrocenemonocarboxylic acid was hydrolyzed to the acid, and, like diphenylcarbamylferrocene, was acylated readily with acetyl chloride and $AlCl_3$. The acetyl derivative of ferrocene monocarbox-

---

[1] Supported in part by a grant from the University of North Carolina Research Council and in part by a du Pont Summer Research Grant (1958).

[2] R. J. Reynolds Research Fellow, 1958–1959.

[3] R. B. Woodward, M. Rosenblum and M. C. Whiting, THIS JOURNAL, **74**, 3458 (1952).

[4] V. Weinmayr, *ibid.*, **77**, 3009 (1955).

[5] M. Rosenblum, Ph.D. Thesis, Harvard University, August, 1953.

[6] R. A. Benkeser, D. Goggin and G. Schroll, THIS JOURNAL, **76**, 4025 (1954).

[7] A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and O. A. Nesmeyanova, *Doklady Akad. Nauk, S.S.S.R.*, **97**, 459 (1954).

[8] D. W. Mayo, P. D. Shaw and M. Rausch, *Chemistry & Industry*, 1388 (1957); M. Rausch, M. Vogel and H. Rosenberg, *J. Org. Chem.*, **22**, 900 (1957).

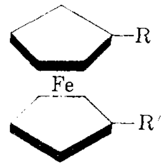
[9] G. T. Morgan and E. A. Coulson, *J. Chem. Soc.*, 2323 (1931).

[10] E. Lellman and O. Bonhoffer, *Ber.*, **20**, 2118 (1887).

[11] L. Gattermann, *ibid.*, **32**, 1116 (1899).

Table I

Derivatives of Carboxylic Acids and Amides of Ferrocene



					Analyses, %					
					Calcd.			Found		
R	R′	M.p., °C.	Yield, %	Formula	C	H	N	C	H	N
$CON(C_6H_5)_2$	H	184–186	64	$C_{23}H_{19}NOFe$	72.46	5.02	3.67	72.70	5.11	3.73
								72.38	4.82	3.46
$CON(C_6H_5)_2$	$CON(C_6H_5)_2$	250 (dec.)	8.3	$C_{36}H_{28}N_2O_2Fe$	...	...	4.86	...	...	4.69
$CON(C_6H_5)_2$	$COCH_3$	140–141	74	$C_{25}H_{21}NO_2Fe$	70.93	5.00	3.31	70.89	5.02	3.53
COOH[a]	$COCH_3$	155–157	86	...	...	...	...	...	...	...
$CON(C_6H_5)_2$	COC_6H_5	136–136.5	71.5	$C_{30}H_{23}NO_2Fe$	...	...	2.89	...	...	2.87
COOH	COC_6H_5	125–126	74	$C_{18}H_{14}O_3Fe$	64.70	4.22	...	65.07	4.38	...
$CONH_2$[b]	H	168.5–171	70.5	...	...	...	...	...	...	...
$CONH_2$	$COCH_3$	151.5–152	61	$C_{13}H_{13}NO_2Fe$	57.59	4.83	5.17	58.05	4.62	5.02
								58.05	4.88	5.02
COOH	H	210 dec.	71.5[c] 40[d]	...	...	...	...	...	...	...

[a] A. N. Nesmeyanov and O. A. Reutov, *Doklady Akad. Nauk, S.S.S.R.*, **115**, 518 (1957). [b] F. S. Arimoto and A. C. Haven, Jr., This Journal, **77**, 6295 (1955). [c] Over-all from ferrocene. [d] Hydrolysis of ferrocene monocarboxamide.

amide resisted hydrolysis under the conditions that were successful for the unsubstituted amide and the diphenylcarboxamides IVa and IVb. It is interesting that these amides can be hydrolyzed in view of the reports[12,13] of the resistance of N-phenylcarbamylferrocene to hydrolysis by either acidic or basic conditions.

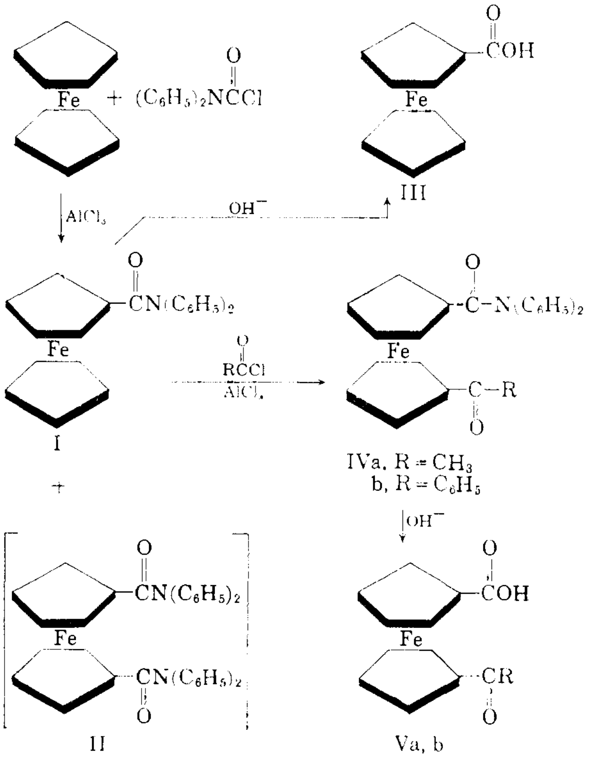


Fig. 1.

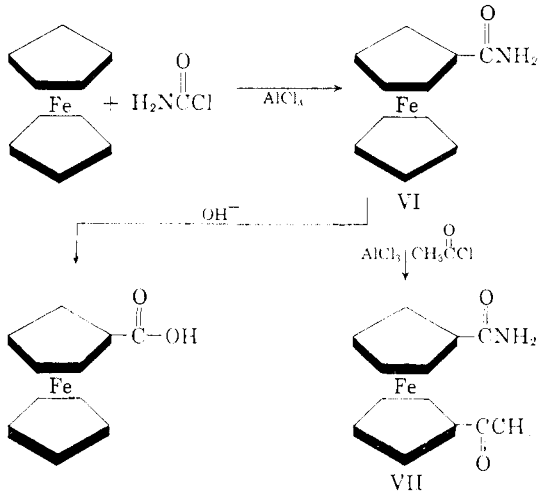
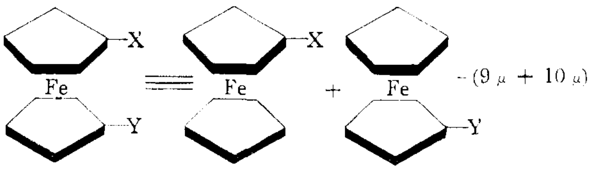


Fig. 2.

Infrared Spectra.—The infrared spectra of these derivatives are interesting in the light of the observation, pointed out by Rosenblum,[14] that the spectrum of a heteroannular disubstituted ferrocene is the sum of the spectra of the corresponding monosubstituted ferrocenes, minus the peaks at 9 and 10 μ



This generalization has proved useful in the present work. Table II shows that this rule holds for all the compounds studied.

Experimental

Melting points are corrected. Most of the analyses are by Weiler and Strauss, Oxford, England.

Preparation of Diphenylcarbamylferrocene.—To a mixture of 13.3 g. (0.1 mole) of aluminum chloride and 100 ml. of ethylene chloride under nitrogen was added a solution of 23.1 g. (0.1 g.) of diphenylcarbamyl chloride in 100 ml. of

---

(12) N. Weliky and E. S. Gould, This Journal, **79**, 2742 (1957).

(13) M. Rausch, P. Shaw, D. Mayo and A. M. Lovelace, *J. Org. Chem.*, **23**, 505 (1958).

(14) M. Rosenblum, *Chemistry & Industry*, 953 (1958).

TABLE II

PRINCIPAL ABSORPTION IN THE INFRARED SPECTRA OF SUBSTITUTED FERROCENES BETWEEN 5 AND 11 μ

R	R'	Peaks
$COCH_3$	H	6.03, 6.90, 7.29, 7.40, 7.84, 9.00, 9.05, 9.67, 9.80, 9.99, 10.42
COC_6H_5	H	6.15, 6.29, 6.37, 6.95, 7.31, 7.52, 7.80, 8.58, 9.06, 9.55, 9.76, 9.99, 10.50
COOH	H	5.84, 5.99, 6.79, 7.16, 7.75, 8.61, 9.04, 9.75, 9.97, 10.92
$CON(C_6H_5)_2$	H	6.13, 6.30, 6.75, 6.98, 7.20, 7.30, 7.52, 7.61, 7.72, 8.87, 9.07, 9.34, 9.75, 9.99
$CONH_2$	H	6.05, 6.35, 6.87, 7.25, 7.54, 8.56, 9.09, 9.70, 9.80, 10.00, 11.02
$COCH_3$	$CON(C_6H_5)_2$	6.05, 6.31, 6.75, 6.94, 7.30, 7.50, 7.60, 7.72, 7.87, 8.87, 9.00, 9.34, 9.67, 9.75, 10.40
$COCH_3$	COOH	5.87, 6.00, 6.80, 6.92, 7.20, 7.30, 7.41, 7.87, 8.61, 9.00, 9.67, 9.76, 10.40, 10.95
$COCH_3$	$CONH_2$	6.02, 6.31, 6.82, 6.90, 7.25, 7.30, 7.40, 7.50, 7.85, 8.54, 8.99, 9.66, 9.78, 10.40, 11.00
COC_6H_5	$CON(C_6H_5)_2$	6.11, 6.28, 6.72, 6.91, 7.30, 7.50, 7.70, 7.80, 8.55, 8.83, 9.30, 9.50, 9.96, 10.46, 11.30
COC_6H_5	COOH	5.87, 5.98, 6.12, 6.28, 6.37, 6.80, 6.94, 7.20, 7.31, 7.51, 7.82, 8.60, 8.75, 9.00, 9.55, 9.75, 10.50, 10.96
$CON(C_6H_5)_2$	$CON(C_6H_5)_2$	6.14, 6.32, 6.77, 6.98, 7.32, 7.55, 7.63, 7.75, 8.32, 8.87, 9.36, 9.75, 10.00

ethylene chloride, with subsequent dropwise addition of a solution of 18.6 g. (0.1 mole) of ferrocene over a 10-minute period. The reaction mixture was held at reflux for 14 hours under nitrogen. Decomposition of the aluminum chloride complex with 100 ml. of water yielded an organic layer which, after washing until neutral to litmus and drying with sodium sulfate, was chromatographed on alumina. The broad orange band was eluted with 1:3 acetone–methylene chloride, and the eluent on evaporation yielded 24.3 g. (63.8%) of the amide. Recrystallization from petroleum ether gave a product melting at 184–186°.

Direct Preparation of Ferrocenemonocarboxylic Acid.—Ferrocenemonocarboxylic acid was prepared in 71.5% yield, based on ferrocene, by the above procedure without isolating the diphenylcarbamylferrocene. The solvent of the organic layer from the Friedel–Crafts reaction was removed and the residue was taken up in 20% ethanolic potassium hydroxide and was allowed to reflux for 18 hours. After evaporation of the solvent, the reaction mixture was dissolved in water and was acidified with concd. hydrochloric acid. The crude acid precipitated on cooling and was purified by dissolving in 5% sodium hydroxide, treating with charcoal, and reprecipitating with HCl. Recrystallization from benzene–petroleum ether yielded bronze needles melting with decomposition at 210° (reported[5] m.p. 210°).

1,1'-Bis-diphenylcarbamylferrocene.—An attempt was made to introduce two diphenylcarbamyl groups into the ferrocene nucleus by the procedure described above for diphenylcarbamylferrocene, using two molar equivalents of diphenylcarbamyl chloride and aluminum chloride per mole of ferrocene. The reaction product was predominantly diphenylcarbamylferrocene. A small amount of bis-diphenylcarbamylferrocene (8.3%, based on ferrocene) was obtained as a yellow powder from the eluent after chromatography. Though the two compounds were not separable by chromatography, fractional crystallization from methylene chloride provided the separation, the disubstituted ferrocene being much less soluble than diphenylcarbamylferrocene.

Bis-diphenylcarbamylferrocene is practically insoluble in most organic solvents. It dissolves in concd. sulfuric acid to give a red color. Recrystallization was effected from a chloroform–ethanol mixture to give yellow crystals melting at 250° dec.

Attempted hydrolysis of this compound in 10% potassium hydroxide in ethanol was unsuccessful, presumably due to the insolubility of the material in the solvent.

1-Acetyl-1'-diphenylcarbamylferrocene.—Diphenylcarbamylferrocene was acetylated by adding a solution of 1.2 g. (15 millimoles) of acetyl chloride in 100 ml. of ethylene chloride dropwise to a mixture of 4.0 g. (30 millimoles) of aluminum chloride and 5.7 g. (15 millimoles) of diphenylcarbamylferrocene in 100 ml. of ethylene chloride at −30° under nitrogen. Over a 60-minute period the reaction mixture was stirred and allowed to warm up to 0°. After stirring an additional 30 minutes at 0°, the reaction mixture was worked up similarly to the procedure described above for diphenylcarbamylferrocene.

A yield of 4.7 g. of orange-red needles (74%) was obtained. After recrystallization from petroleum ether, the melting point was 140–141°.

Acetyldiphenylcarbamylferrocene dissolves in concd. HCl to give a deep red solution.

An attempt to prepare 1-acetyl-1'-diphenylcarbamylferrocene by the action of diphenylcarbamyl chloride on acetylferrocene gave only recovery of the acetylferrocene.

1-Acetyl-1'-ferrocenecarboxylic Acid.—1-Acetyl-1'-diphenylcarbamylferrocene (2.0 g.) was dissolved in 35 ml. of 10% ethanolic KOH and was allowed to reflux for 5 hours. Concentration of the mixture to 25 ml. and cooling yielded crystals of diphenylamine, m.p. 53–55°; mixed melting point with an authentic sample of diphenylamine showed no depression. The filtrate on acidification and extraction with ether yielded 1.29 g. of crude 1-acetyl-1'-ferrocenecarboxylic acid, m.p. 149–156.5°. Recrystallization from benzene gave 1.11 g. (86.4%) of red needles melting at 155–157° (reported m.p. 153–155°; (Table I, ref. *a*)). The acid is readily soluble in aqueous base and also in concentrated HCl and is slightly soluble in water.

1-Benzoyl-1'-diphenylcarbamylferrocene was prepared by a procedure similar to that given above for 1-acetyl-1'-diphenylcarbamylferrocene except for the inverse addition of a solution of diphenylcarbamylferrocene to a mixture of benzoyl chloride and aluminum chloride at −30°. The reaction period included one hour at −30° and 5.5 hours at 0°. The product was recrystallized from acetone to yield 8.7 g. (71.5%) of orange crystals, melting at 136–136.5°, from 9.5 g. of diphenylcarbamylferrocene.

1-Benzoyl-1'-diphenylcarbamylferrocene is slightly soluble in concd. hydrochloric acid and dissolves in concd. sulfuric acid to give a blue solution.

1-Benzoyl-1'-ferrocenecarboxylic acid was prepared by hydrolysis of 1-benzoyl-1'-diphenylcarbamylferrocene by a procedure identical to that described above for 1-acetyl-1'-ferrocenecarboxylic acid. Recrystallization from benzene gave 2.04 g. (74%) of red crystals melting at 125–126° from 4.00 g. of 1-benzoyl-1'-diphenylcarbamylferrocene. This acid is readily soluble in aqueous base and slightly soluble in concd. hydrochloric acid. In sulfuric acid it gives a blue color.

Carbamylferrocene.—Carbamyl chloride, obtained by pyrolysis of 6.5 g. (0.05 mole) of cyanuric acid in a stream of dry HCl,[11] was introduced into a suspension of 10 g. (0.075 mole) of aluminum chloride in 150 ml. of ethylene chloride at 0°. Concurrently, a solution of 9.3 g. (0.05 mole) of ferrocene in 200 ml. of ethylene chloride was added to the mixture. Twenty minutes was allowed for the additions, and one hour for the mixture to warm to room temperature; the mixture was stirred for 16 hours under nitrogen at room temperature. The aluminum chloride complex was decomposed with 100 ml. of water, and the organic phase was washed with water, dried with sodium sulfate, and evaporated to a residue which was washed with petroleum ether. A yellow solid (8.8 g.) was thus obtained that was recrystallized from chloroform–petroleum ether to yield 8.1 g. (70.5%) of brown needles, m.p. 168–171° (lit. m.p. of ferrocene monocarboxamide, 168–170°; Table I, ref. *b*).

Hydrolysis of Carbamylferrocene.—Carbamylferrocene (2.00 g.) was hydrolyzed in 35 ml. of 15% ethanolic KOH containing a few drops of water at reflux for 12 hours. Dilution with 250 ml. of water yielded a small recovery of the amide (0.21 g.), and acidification and cooling of the filtrate gave after purification 0.80 g. (40%) of yellow needles, m.p. 201–204°; mixed melting point with an authentic sample of ferrocenoic acid (m.p. 210° dec.), 204–206°.

1-Acetyl-1′-carbamylferrocene was prepared by a procedure essentially identical to that described above for 1-acetyl-1′-diphenylcarbamylferrocene. From 4.6 g. (20 millimoles) of carbamylferrocene was obtained 3.2 g. (61%) of the acetylcarbamylferrocene as orange-red crystals (from benzene) melting at 151–152°.

Attempted hydrolysis of 1-acetyl-1′-carbamylferrocene in 10–15% ethanolic potash, acetic–hydrochloric acid mixtures, concentrated hydrochloric acid, and sulfuric acid containing sodium nitrite gave only intractable tars.

CHAPEL HILL, N. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

The Constitution of Organoberyllium Halides

BY RAYMOND E. DESSY

RECEIVED AUGUST 3, 1959

Exchange in the system $(C_6H_5)_2Be \cdot Be^*Br_2 \rightleftarrows (C_6H_5)_2Be + Be^*Br_2 \rightleftarrows 2C_6H_5Be^*Br$ has been investigated using Be^7 as a tag. Results show that there is no exchange of Be between the two species $(C_6H_5)_2Be$ and $BeBr_2$, and indicate that there is no such structure as C_6H_5BeBr.

It has been made increasingly clear, over the last few years, that equilibria of the Schlenk type

$$R_2M + MX_2 \rightleftarrows 2RMX \qquad (1)$$

used to represent the structure in solution of organometallic compounds of the Group II metals are not universal. By use of radioactive tracers it has been shown[1] that where M = Mg, and R = Et, C_6H_5, there is no exchange of Mg between R_2Mg species and Mg^*X_2 species, thus indicating the non-existence of RMgX. Similarly, Garrett[2] has reported that where M = Cd and R = Et there is no evidence for exchange of Cd between R_2Cd species and CdX_2 species.

The existence of the species $R_2Cd \cdot CdX_2$ receives support from equilibrium constant measurements and molecular weight determinations. Preliminary data[2] involving measurements of equilibrium constants in the system M = Zn and R = Et also indicate the non-existence of the RZnX species.

On the other hand, there is little doubt that in the system M = Hg, and R = alkyl, aryl that a species such as RHgX does exist—it is isolable, and molecular weights indicate a monomer. In most solvents the equilibrium appears to be almost quantitatively to the right. Rate measurements have been made on the system, and a mechanism for the reaction has been proposed.[3,4]

It thus appears that there is only one demonstrable case of the existence of an RMX compound. Beryllium seemed to provide the most important additional test case.

The normal reaction between an alkyl halide and beryllium metal apparently cannot be used to form an organoberyllium halide.[5] Gilman has succeeded[6] in preparing ether solutions of substances described as organoberyllium halides by reaction of RX compounds and Be metal in the presence of $HgCl_2$ as a catalyst under high pressure and temperature. No analytical data were reported.

Gilman also has pointed out[7] that solutions of dialkylberyllium react with an excess of beryllium chloride to give a solution "with the characteristics" of "organoberyllium halides." Apparently all that is known about the differential behavior of dialkylberyllium compounds and "organoberyllium halides" is that the former react more rapidly with Michler ketone.[8] It also has been shown[8] that thermal decomposition of the materials termed organoberyllium halides leads to the formation and evolution of dialkylberyllium compounds. All of this evidence for the existence of RBeX is speculative.

Coates[9] reports that although $(CH_3)_2Be$ reacts with methanol explosively, the reaction with HCl requires long periods of heating. The gas evolved was identified as methane, and the white solid remaining was assumed to be methylberyllium chloride ($\log P_{mm} = 6.52 - 2614/T$; *cf.* $(CH_3)_2Be$ where $\log P_{mm} = 13.29 - 5100/T$).

In light of the scant knowledge as to the existence of organoberyllium halides, it was felt that an investigation of exchange in the system

$$R_2Be \cdot Be^*X_2 \rightleftarrows R_2Be + Be^*X_2 \rightleftarrows 2RBe^*X \qquad (2)$$

would be of value. For practical reasons, R was chosen to be phenyl and X bromine.

Experimental

Beryllium Metal.[10]—Cyclotron target material having the analysis (spectrographic) given was used: Al,

---

(1) Raymond E. Dessy and G. S. Handler, THIS JOURNAL, **80**, 5824 (1958).

(2) A. B. Garrett, Arthur Sweet, W. L. Marshall, David Riley and Anis Touma, *Rec. Chem. Progress*, 155 (1952).

(3) Raymond E. Dessy and Y. K. Lee, THIS JOURNAL, **82**, 689 (1960).

(4) In a paper by I. B. Johns and R. M Hixon (*J. Phys. Chem.*, **34**, 2226 (1930)) in which measurements of the equilibrium constant for the above reaction were measured by e.m.f. studies on the cell

$$\begin{array}{lllll} & HgI_2\ 0.005\ M & & R_2Hg + HgI_2 \rightleftarrows 2RHgI & \\ Hg\ | & KI\ 0.05 M & \| & KI\ 0.05\ M & |\ Hg \\ & EtOH & & EtOH & \end{array}$$

it was concluded that in the series R = Me, Et, *n*-Bu the equilibrium constant was of the order of 100, but when R = C_6H_5 of the order of 1. It seems apparent that their assumptions that the junctions RHgI/Hg and R_2Hg/Hg are zero are invalid. Although the experimental technique looks promising, further work apparently is necessary.

(5) Henry Gilman, THIS JOURNAL, **45**, 2693 (1923).

(6) Henry Gilman and F. Schulze, *ibid.*, **49**, 2904 (1927).

(7) Henry Gilman and F. Schulze, *J. Chem. Soc.*, 2663 (1927).

(8) Henry Gilman and F. Schulze, THIS JOURNAL, **49**, 2904 (1927).

(9) G. E. Coates, F. Glockling and N. D. Huck, *J. Chem. Soc.*, 4512 (1952).

(10) All handling of beryllium metal should follow the suggestions laid down in the pamphlet "Some Notes on Safe Handling Practices for Beryllium," distributed by the Defense Metals Information Center, Battelle Memorial Institute.