Summarizing the discussions above, in 1-benzyl-1,2,3,4-tetrahydroisoquinoline system, necessary requirements for being in the conformational state drawn in Fig. 1, *i.e.*, for diamagnetic ring current of the benzyl-benzene to affect C(8)-protons positively, are presence of methylimino and 7-alkoxyl groups. Influence of 6- and 4′-substituents is negligible, and in case of 7-hydroxyl, the effect is in a smaller extent though detectable. Further, introduction of the substituents at C(8)-position of the system, results in the appearance of diamagnetic effect of the benzyl-benzene ring of the methylimino protons, and the direction of the effect turns reverse.

These experimental data and conclusions derived therefrom, lead to a conviction that the assignment of the alkoxyl groups to their chemical shifts is unequivocally accomplished in the N-methylcoclaurine series, and the contribution of the NMR spectral studies to the structure elucidation of the biscoclaurine alkaloids will be of greater extent.

The authors' thanks are due to Prof. E. Fujita of the Institute for Chemical Research, this University, for his generous gift of a new compound, 1-(4-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline, prior to his publication.

Summary

The proton magnetic resonance spectra of N-methylcoclaurine type bases were examined and assignment of the alkoxyl groups and aromatic protons was presented. Correlations of the chemical shifts with stereochemistry of the molecule were discussed.

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120. Keiichi Tanikawa and Kiichi Arakawa : Organometallic Compounds. IV.[*1] Analytical Determination of Ferrocene Derivatives by Gas Chromatography.[*2]

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As a series of studies to separate and analyze organometallic compounds by gas chromatography, the authors reported on "Gas Chromatography of Metal Acetylacetonates" in the previous paper,[1] and gas chromatographic analyses of ferrocene derivatives will be reported in the present paper.

Analyses and determinations of purity of the ferrocene derivatives have been made by means of infrared absorption spectra,[2] thin-layer chromatography,[3] and nuclear magnetic resonance.[4]

[*1] Part Ⅲ. K. Yamakawa, N. Ishibashi, K. Arakawa : This Bulletin, **12**, 119 (1964).

[*2] Presented at the 13th Annual Meeting of Japan Society for Analytical Chemistry. Sept. 29, 1964 (Sendai).

[*3] 1618 Ida, Kawasaki, Kanagawa Ken (谷川啓一, 荒川基一).

1) K. Yamakawa, K. Tanikawa, K. Arakawa : This Bulletin, **11**, 1405 (1963).

2) K. Schlogl, H. Pelonsek, A. Mohar : Monatsh. Chem., **92**, 533 (1961).

3) A review, see H. P. Fritz in F. G. A. Stou, and R. West ed., "Advances in Organometallic Chemistry," Vol. 1, p. 262, Academic Press, New York (1964).

4) M. Rosenblum, *et al.* : J. Am. Chem. Soc., **85**, 316 (1963); K. L. Rinehart, *et al.* : *Ibid.*, **85**, 970 (1963) : Y. Nagai, *et al.* : Bull. Chem. Soc. Japan, **37**, 53 (1964); M. L. Levenberg, J. H. Richards : J. Am. Chem. Soc., **86**, 2634 (1964).

Recently, Benkeser and co-workers5~8) reported the separations and analyses of the ferrocene derivatives by gas chromatography. In parallel with their work, several ferrocene derivatives, which were synthesized in the authors' laboratory, were successfully separated by gas chromatography.

The reaction products of ferrocene formed by various reactions are different by catalysts and reaction conditions employed, and in addition to mono-substituted (1-position) and di-substituted derivatives, a small amount of 1,2- and 1,3-di-stbstituted derivatives, are obtained. The products are stable for heat, and it it convenient for gas chromatographic separation. Benkeser and co-workers6) reported that methyl-, ethyl-, iso-propyl-, and *t*-butylferrocene were synthesized in order to examine the reactivities of these substituted ferrocenes, and these alkylferrocenes were acetylated with acetic anhydride in dichloromethane competitively with ferrocene. They determined the amounts of thus formed acetylferrocene and each isomer of acetylalkylferrocenes (1,1′-, 1,2-, 1,3-disubstituted ferrocenes) by gas chromatography. The analyses were carried out with DEGS under the conditions of 15 ft. × 0.25 in. column at 215°. At the same time, the separation of triethylsilylisopropylferrocene, 1-*t*-butyl-1-triethylsilylferrocene and 1-methyl-1′-triethylsilylferrocene were carried with Apiezon-L column, 16 ft. × 0.25 in., at 280°, 290°, and 290° respectively.

In the authors' laboratory, on the other hand, the separation of the mixture of ferrocene derivatives were successively carried out with a column in which chromosorb-W or glassmicrobeads properly coated with Apiezon-L or silicon rubber was packed.

In the following section, various results are described.

Experimental

Sample——The following compounds were synthesized in the authors' laboratory: Ferrocene,9) 1,1′-diacetylferrocene,9) dimethyl 1,1′-ferrocenedicarboxylate,9) acetylferrocens,10) ferrocenemethanol,11) 1,1′-ferrocenedimethanol,12) ferrocenemercury chloride,13) iodoferrocene,14) and phenylferrocene.15)

Preparation of the Column——Apiezon-L or silicon rubber is weighed, and appropriate amount in weight % for the fixed phase is dissolved in toluene (Note: these substances may be dissolved in acetone

Table I. Gas Chromatography Column[*4]

Column A: packed with 1% SE-30 on chromosorb-W
Column B: packed with 0.5% SE-30 on glassmicrobeads
Column C: packed with 1% SE-52 on glassmicrobeads
Column D: packed with 2.5% SE-52 on glassmicrobeads
Column E: packed with 1% PEGS on chromosorb-W
Column F: packed with 2.5% PEGS on chromosorb-W
Column G: packed with 2.5% PEG-6000 on chromosorb-W
Column H: packed with 2.5% Apiezon-L on chromosorb-W

[*4] PEGS: polyethylene glycol succinate. PEG-6000: polyethylene glycol, mol. wt. 6000.

5) R.A. Benkeser, J.L. Barch: J. Am. Chem. Soc., **86**, 890 (1964).
6) R.A. Benkeser, Y. Nagai, J. Hooz: *Ibid.*, **86**, 3742 (1964).
7) Y. Nagai, J. Hooz, R.A. Benkeser: Bull. Chem. Soc. Japan, **36**, 482 (1964).
8) Y. Nagai, R.A. Benkeser, J. Hooz: 17th Annual Meeting Chem. Soc., Japan, Abst. papers 1 G 19, April, 1964, Tokyo.
9) K. Yamakawa, H. Ochi, K. Arakawa: This Bulletin, **11**, 905 1963).
10) V. Weinmyr: J. Am. Chem. Soc., **77**, 3009 (1955).
11) A.N. Nesmeyanov, *et al.*: Doklady Akad. Nauk SSSR., **112**, 439 (1957).
12) S. Okawara, *et al.*: Kogyo Kagaku Zasshi, **65**, 685 (1962).
13) D.M. Rausch, Heringer: J. Org. Chem., **22**, 900 (1959).
14) H. Shechter, J.H. Helling: J. Org. Chem., **26**, 1034 (1961).
15) V. Weinmyr: J. Am. Chem. Soc., **77**, 3012 (1955).

and other organic solvents, but when the substance is dissolved in such organic solvents having low boiling point, the solvent is evaporated before the fixed phase is coated uniformely when the both are mixed, and it may be a cause of the tailing).

The toluene solution of the coating substance and the fixed phase are transferred into an egg-shaped flask together, and toluene is completely removed in a rotary evaporator under reduced pressure with heating on a water bath to make the packing agent. Eight different columns were used for the purpose of the separation, and these are shown in Table I.

Apparatus and Method——Shimadzu Gas Chromatograph Model GC-1B (dual column) was for the separations and a thermal conductivity cell detector was used. Range 2.0 mV, and 200 mA of the filament current were the conditions of the measurements.

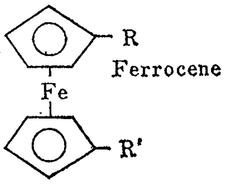
Stainless column, 140 cm. (70 cm. U-shape × 2) × 4 mm. i.d. was used, but 210 cm. × 4 mm. i.d. stainless column was used in the Column C. The amount of coating on the fixed phase liquid is sufficient in 0.5∼2.5%. The purification of the fixed phase is referred to the preceeding report.[1]

The conditions of the column are as follows: Temperature should be at 170∼200°, and the sample heater and the detector temperature should be kept 30° and 40° higher the column temperature respectively. He is used as a carrier gas and introduced into a column in 30∼100 ml./min. Samples, the ferrocene derivatives, were generally dissolved in chloroform in 3∼4%, and 2∼3 μl. of the sample were injected.

Results and Discussion

The ferrocene derivatives are generally stable for heat and some of them are sublimated, therefore, gas chromatographic procedures of them are easily carried out. In order to select the column temperature for the separation, the temperature is raised from the melting point of the sample to a certain temperature, and the most suitable temperature*[5] to separate ferrocene derivatives was 200° and the samples on Table II could be separated.

TABLE II. Retention Time of Ferrocene Derivatives



	m.p. (°C)	Retention time (min.) A	B	C	D	E	F	G	H
$R=R'=H$	171∼173	1.36	0.94	1.24	1.23	1.05	0.76	0.60	0.90
$R=COCH_3$, $R'=H$	82∼83	4.55	2.67	3.55	4.26	8.00	4.76	4.51	2.66
$R=R'=COCH_3$	122∼124	13.57	7.32	10.54	14.35	60.00	33.57	28.17	8.00
$R=R'=COOCH_3$	112∼113	12.03	8.30	10.12	13.48	29.90	15.48	16.00	6.57
$R=R'=CH_2OH$	108.5∼109.5	4.00	2.60	3.10	4.10	4.68	2.84	2.86	2.91
$R=HgCl$, $R'=H$	192∼193	2.12	1.42	1.67	2.00	1.65	1.16	1.06	1.36
$R=I$, $R'=H$	43∼44	3.94	2.62	2.95	3.73	3.30	2.03	2.45	2.94
$R=Ph$, $R'=H$	107∼108	12.45	8.00	9.30	12.93	13.58	7.41	9.30	9.90

When a single sample is handled with gas chromatography, the column temperature should be 10∼20° lower than the indicated column temperature (for example, ferrocene, ferrocenemercury chloride, iodoferrocene) or higher than the indicated temperature (namely, 1,1'-diacetylferrocene, dimethyl 1,1'-ferrocene dicarboxylate, phenylferrocene) to obtain better results, but when the subject is the mixed derivatives, the column temperature should be selected in order to obtain good results of each chromatogram.

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*[5] When column H was used, the column temperature was 200°, and 190° in columns A, B, F, G, 170° in columns C and E, and 180° in column D.

The retention times of ferrocene and ferrocene mercury chloride are shorter in the columns A~H, as a whole, particularly in columns F and G, the retention times were (0.76, 1.16) respectively.

The separation in the column C, different from other columns, was carried out using 2.1 m. × 4 mm. column, since under the condition of 1.4 m. × 4 mm. at 190°, the retention time was generally a little too short, and the changing condition ended up with a good result in the column C (1% SE-52 on glassmicrobeads).

Carefully examining the results of Benkeser and co-workers, they used 16 ft. × 0.25 in. column at 240~280°, that is, they use the same column, Apiezon-L, but longer column and higher temperature were employing, so that they used 3.5 times longer column and 80° higher temperature. A 15 feet-column was used in case of DEGS. When silicon rubber was employed, the length of the column was 4 ft., and the temperature was 160°, the same conditions with other cases.

Separation of the Mixture of Ferrocene Derivatives

The results of separating of several ferrocene derivatives by gas chromatography are shown in Fig's. 1~4. Symmetrical chromatograms were obtained with any of columns A~H when ferrocene and phenylferrocene were separated. The results obtained when the separation was carried out using columns A, F, and H are compared in Fig. 1. The first peak which is scaling out is the solvent, chloroform. The next peaks, indicated as a, a′, and a″ correspond to ferrocene (0.76, 0.90, and 1.36 respectively) and b, b′, and b″ correspond to phenylferrocene (7.41, 9.90, and 12.45 respectively).

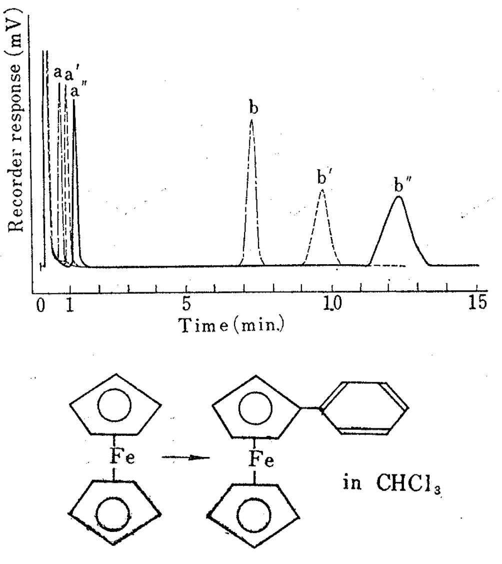

Fig. 1. Separation of a Mixture of Ferrocene and Phenylferrocene

———— A 1% SE-30 on chromosorb-W
- - - - - H 2.5% Apiezon-L on chromosorb-W
———— F 2.5% PEGS on chromosorb-W

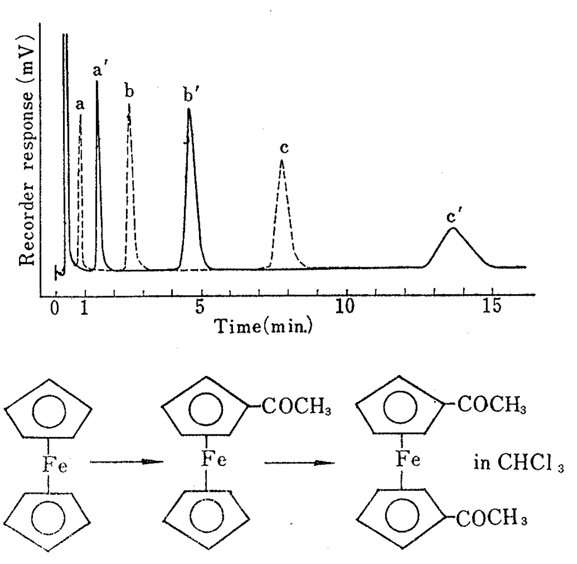

Fig. 2. Separation of a Mixture of Ferrocene, Acetylferrcene and 1,1′-Diacetylferrocene

———— A 1% SE-30 on chromosorb-W
- - - - - H 2.5% Apiezon-L on chromosorb-W

During the process of acetylation of ferrocene, acetylferrocene and 1,1′-diacetylferrocene are formed,[16] and the mixture of the two was separated by gas chromatography, and the chromatogram is shown in Fig. 2. Any columns, from A to H, could separate the mixture of ferrocene and acetylferrocene derivatives beautifully. The chromatograms shown in the figure are those obtained by the columns A and H, and the both show symmetrical beautiful peaks. The first appearing peak is corresponded

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[16] G. D. Broadhard, J. M. Osgerby, P. L. Pauson: J. Chem. Soc., 650 (1958).

to the solvent, chloroform, and the next coming peaks are those of ferrocene, a, a′ (0.90 and 1.36 respectively), monoacetylferrocene, b, b′ (2.66 and 4.55) and 1,1′-diacetylferrocene, c, c′ (8.00 and 13.57). During the synthetic process of 1,1′-ferrocene dimethanol from ferrocene,[2] the starting material, ferrocene, and the intermediates, 1,1′-diacetylferrocene and dimethyl 1,1′-ferrocene dicarboxylate are slightly mixed in the product, and the separating chromatograms are shown in Fig. 3. The separation was carried out with the column H, and symmetrical beautiful curves are obtained. The first peak is corresponded to the solvent, chloroform. The next detected peaks are; a, ferrocene (0.90), b, 1,1′-ferrocene dimethanol (2.91), c, dimethyl 1,1′-ferrocene dicarboxylate (6.57), and d, 1,1′-diacetylferrocene (8.00), respectively.

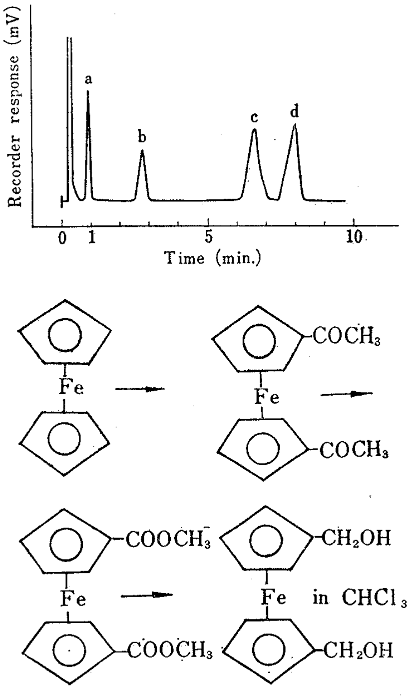

Fig. 3. Separation of a Mixture of Ferrocene, 1,1′-Diacetylferrocene, Dimethyl 1,1′-Ferrocenedicarboxylate, and 1,1′-Ferrocenedimethanol.

——— H 2.5% Apiezon-L on chromosorb-W

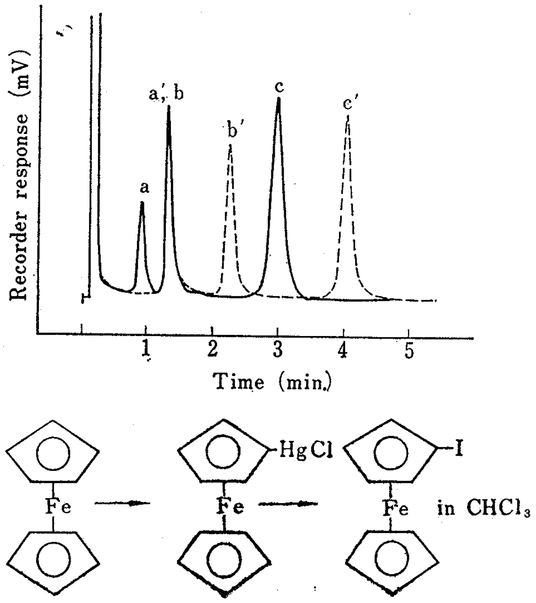

Fig. 4. Separation of a Mixture of Ferrocene, Ferrocene-mercury Chloride and Iodoferrocene

- - - - - A 1% SE-30 on chromosorb-W

——— H 2.5% Apiezon-L on chromosorb-W

Condition :

column temp.	A) 190°, H) 200°
sample heater	A) 220°, H) 230°
detector temp.	A) 230°, H) 240°
carrier gas He	A) 80 ml./min. H) 50 ml./min.

During the synthetic process of biferrocenyl,[3] ferrocene, the starting material, and the intermediates, ferrocenemercury chloride and iodoferrocene are mixed in the product, and these are separated by gas chromatography, and the results are shown in Fig. 4. The retention time was short when any of columns A~H were used. Distance between each peaks are close one another, but the separation was satisfactorily carried out. The result of separation by columns A and H is shown in the figure, and the chromatogram shows symmetrical curves. The first scaling-out peak is corresponded to the solvent, chloroform, and the following peaks are those of ferrocene, a and a′ (0.90 and 1.36 respectively), ferrocenemercury chloride, b and b′ (1.36 and 2.12) and iodoferrocene, c and c′ (2.94 and 3.94). The separation of the illustrated ferrocene derivatives could not be carried out satisfactorily except with column H. Namely, a part of peaks of dimethyl 1,1′-ferrocene dicarboxylate and 1,1′-diacetylferrocene are overlapped when columns A, C, and D were employed. Retention time of 1,1′-diacetylferrocene is delayed when columns E and F were used, and these are not suitable for the separation.

From the results hitherto mentioned, it was shown that the mixture of several ferrocene derivatives shown in Fig's. 1, 2, and 4 could be separated by any of columns A~H in Table I, but the separation of mixture of ferrocene derivatives in Fig. 3 could be achieved only by column H.

The authors wish to express their hearty thanks to Dr. S. Mizushima of this laboratory who always encouraged them to conduct this work. The authors also thank to H. Ochi and N. Ishibashi who helped the synthetic experiments, to Dr. K. Yamakawa of Tokyo College of Science who discussed with them on many problems.

Summary

The satisfactory results were obtained to separate the mixture of several ferrocene derivatives by gas chromatography using column H (2.5% Apiezon-L on chromosorb-W, column length 1.4 m. × 4 mm., column temperature 200° and flow rate of He 50 ml./min.).

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UDC 547.94.07 : 547.836.3.07

121. **Yoshio Ban, Reiji Sakaguchi, and Masako Nagai** (née Seo) :

The Synthesis of β-Carboline Derivatives. VII[*1]. The Isolation of the Possible Intermediate in the Condensation of 3-(2-Bromoethyl)indole and 2-Halogenopyridine.

(*Faculty of Pharmaceutical Sciences, School of Medicine, Hokkaido University*[*2])

In the previous papers of this series,[1] it was reported that the possible intermediates in the new method for the synthesis of β-carboline derivatives developed in this laboratory are isolated only in specific cases. For instane, on condensation of 3-(2-bromoethyl)indole (I) with 3-chloro-5,6,7,8-tetrahydroisoquinoline (Ⅱ), there was obtained 2-[2-(3-indolyl)ethyl]-3-chloro-5,6,7,8-tetrahydroisoquinolinium bromide (Ⅲ) as an intermediate, which was treated with phosphoryl chloride to afford the indoloquinolizinium salt (Ⅳ).

Nevertheless, in the general procedure which I is heated with 2-halogenopyridine (Ⅴa, b) on a water bath for 4~10 hr., 6,7-dihydro-12*H*-indolo [2,3-*a*]quinolizinium salt (Ⅵ) is the sole product although careful search for the possible intermediate (Ⅶ) has been made.[2] In this paper, it is reported that such an intermediate (Ⅶ) has been actually isolated and characterized.

A solution of I and 2-bromopyridine (Ⅴa) in ethanol was allowed to stand at room temperature for one week to produce a quaternary salt as yellow prisms, m.p. 121~122°

[*1] Part Ⅵ. Y. Ban, I. Inoue: This Bulletin, **12**, 1381 (1964).

[*2] Kita-12-jo, Nishi-5-chome, Sapporo, Hokkaido (伴 義雄, 坂口礼司, 永井雅子(旧姓瀬尾)).

1) *a*) Y. Ban, M. Seo: Tetrahedron, **16**, 11 (1961). *b*) Y. Ban, M. Seo: This Bulletin, **12**, 1378 (1964).

2) Y. Ban, M. Seo: Tetrahedron, **16**, 5 (1961).