[Chem. Pharm. Bull. 13(8) 921～926 (1965)]

UDC 547.94.02 : 582.675.4

119. Masao Tomita, Teturo Shingu, Kazuyoshi Fujitani, and Hiroshi Furukawa : Studies on the Alkaloids of Menispermaceous Plants. CCXVI.[*1] Nuclear Magnetic Resonance Spectra of Benzylisoquinoline Derivatives. (1). N-Methylcoclaurine Type Bases.

(Faculty of Pharmaceutical Sciences, Kyoto University[*2])

Among the alkaloids containing 1-benzylisoquinoline system, a series of compound having alkoxyl or hydroxyl groups at 6-, 7-, and 4′-positions of the system, may be classified as N-methylcoclaurine type bases, and aside from a few naturally occurring bases, a majority of the known bases of this class have been found to be the reaction products of alkali metal-ammonia fission of biscoclaurine type (bisbenzylisoquinoline) alkaloids.

After the first application of this reductive fission of biscoclaurine alkaloids into N-methylcoclaurine type bases by Tomita, *et al.*, structure determination of these bisected bases has become a fruitful and inevitable method in the course of the structure elucidation of various biscoclaurine type alkaloids.

Presently, the authors examined the proton magnetic resonance (NMR) spectra of N-methylcoclaurine type bases[*3] and several of related classes, and report here the analyses of the spectra and discussions on the correlation of the chemical shifts with the structural features and stereochemical picture of the molecule of the bases.

Experimental

The NMR spectra were taken on Varian A-60 High Resolution spectrometer on 0.3～2.0 mol. solutions in deuteriochloroform containing tetramethylsilane as an internal reference, at 25～30°. Minor variations in concentration were unimportant. Chemical shifts are expressed in τ values (accuracies ± 0.02 p.p.m.). Chemical shift values of methylene protons of ethoxyl groups are the central position of the quartet, not the position of the center of gravity.

Results and Discussion

In Table I, the chemical shift data for the compounds (I～VI), all bearing 6-, 7-, and 4′-alkoxyl groups are given. Apparently, all of the methoxyl protons have chemical shift values in either of three regions, namely, (A) 6.45～6.49 τ, (B) 6.23～6.25 τ, (C) 6.18～6.20 τ. In the spectra of compounds (III and VI), both having an ethoxyl instead of methoxyl group at 7-position, no signal is found in 6.45～6.49 τ region, and it is quite legitimate that signals in region (A) for the other compounds should be attributable to 7-methoxyl groups. Compounds (II, V, and VI), lacking 4′-methoxyl, present no signal in region (B), and compounds (IV and V) show none at 6.18～6.20 τ, then it is understandable that signals at 6.23～6.25 τ are for 4′- and those in 6.18～6.20 τ are for 6-methoxyls respectively. Further assignments of the signals for methyl and methylene groupings of ethoxyl substituents are given analogously as shown in Table I.

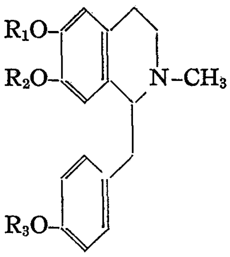
[*1] Part CCXV. M. Tomita, T. Ibuka, Y. Inubushi, K. Takeda : This Bulletin, 13, 704 (1965).

[*2] Yoshida, Sakyo-ku, Kyoto (富田真雄, 新宮徹朗, 冨士谷憲徳, 古川 宏).

[*3] I. R. C. Bick and others reported the NMR spectral data of two species of N-methylcoclaurine type bases in their paper on NMR spectral studies of bisbenzylisoquinolines, but no full assignment of the methoxyl groups is provided. (I. R. C. Bick, J. Harley-Mason, N. Sheppard, M. J. Vernengo : J. Chem. Soc., **1961**, 1902.).

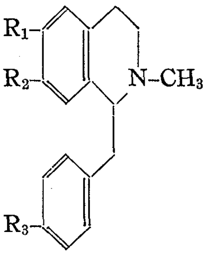
For phenolic compounds (Ⅶ~Ⅻ), above assignment for methoxyl groups must be applied analogously, and the results are summarized in lower column in Table I.

Table I.



R_1	R_2	R_3		Aromatic-H		O-C$\underline{H}_3$			O-C$\underline{H}_2$CH$_3$			N-C$\underline{H}_3$	O-CH$_2$C$\underline{H}_3$		
				C(5)-H	C(8)-H	R_1	R_2	R_3	R_1	R_2	R_3		R_1	R_2	R_3
Me	Me	Me	I[1]	3.45	3.97	6.18	6.45	6.25	—	—	—	7.48	—	—	—
Me	Me	Et	II[2,3]	3.45	3.98	6.18	6.45	—	—	—	6.00	7.47	—	—	8.62
Me	Et	Me	III[*4]	3.45	3.92	6.18	—	6.24	—	6.22	—	7.48	—	8.68	—
Et	Me	Me	IV[3]	3.45	3.97	—	6.45	6.23	5.95	—	—	7.47	8.58	—	—
Et	Me	Et	V[4]	3.47	3.98	—	6.47	—	5.97	—	6.02	7.48	8.57	—	8.61
Me	Et	Et	VI[5]	3.47	3.93	6.20	—	—	—	6.23	6.02	7.48	—	8.68	8.62
Me	Me	H	VII[6]	3.43	4.00	6.18	6.47	—	—	—	—	7.48	—	—	—
Me	Et	H	VIII[7]	3.45	3.97	6.20	—	—	—	6.27	—	7.48	—	8.72	—
Et	Me	H	IX[3]	3.45	4.05	—	6.49	—	5.97	—	—	7.47	8.58	—	—
Me	H	Me	X[5]	3.47	3.65	6.20	—	6.25	—	—	—	7.55	—	—	—
H	Me	Me	XI[8]	3.43	4.07	—	6.47	6.23	—	—	—	7.48	—	—	—
Me	H	H	XII[9]	3.50	3.68	6.20	—	—	—	—	—	7.57	—	—	—

Table II.

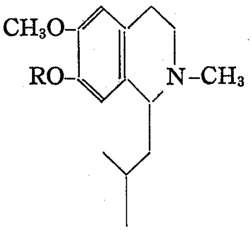


R_1	R_2	R_3		Aromatic-H		O-C$\underline{H}_3$			N-C$\underline{H}_3$
				C(5)-H	C(8)-H	R_1	R_2	R_3	
O-Me	H	O-Me	XIII[10]	3.37	(2H)	6.22	—	6.22	7.50
H	O-Me	O-Me	XIV[10]		3.77	—	6.40	6.22	7.50
O-Me	O-Me	H	XV[11]	3.45	4.03	6.18	6.50	—	7.47
H	OH	O-Me	XVI[10]		3.94	—	—	6.25	7.55
H	O-Me	H	XVII[10,12]		3.82	—	6.45	—	7.50
H	OH	H	XVIII[10,12]		3.97	—	—	—	7.54

[*4] This sample was prepared by ethylation of X with ethereal diazoethane.

1) M. Tomita, E. Fujita, F. Murai: Yakugaku Zasshi, **71**, 1035 (1951).
2) H. Furukawa: *Ibid.*, **85**, 335 (1965).
3) M. Tomita, Y. Okamoto: *Ibid.*, **85**, 456 (1965).
4) M. Tomita, T. Ibuka: *Ibid.*, **85**, 557 (1965).
5) M. Tomita, H. Furukawa, T.H. Yang, T.J. Lin: This Bulletin, **13**, 39 (1965).
6) E. Fujita, F. Murai: Yakugaku Zasshi, **71**, 1043 (1951).
7) M. Tomita, T. Kikuchi: *Ibid.*, **77**, 235 (1957).
8) M. Tomita, Y. Kondo: *Ibid.*, **77**, 1023 (1957).
9) M. Tomita, T. Kikuchi: *Ibid.*, **77**, 997 (1957).
10) Y. Sasaki, H. Ohashi, N. Satoh: This Bulletin, **3**, 178 (1955).
11) J. Niimi: Yakugaku Zasshi, **80**, 1005 (1960).
12) H. Furukawa: *Ibid.*, in press.

TABLE III.



R		Aromatic-H	O-C$\underline{H}_3$	N-C$\underline{H}_3$
Me	XIX[13]	3.47 (2H)	6.15 (6H)	7.55
H	XX[13]	3.47 3.30	6.17	7.57

To interpret the above results that 6-, 7-, and 4′-methoxyl and ethoxyl have respectively different chemical shift values, diamagnetic anisotropy of the benzene ring which constitutes benzyl moiety of the molecule (benzyl-benzene) should be taken into account. Thus, the comparison of the τ values of methoxyl groups of the compounds listed in Table I with those of XIX in Table III which does not possess the benzyl group, shows that both methoxyl groups of XIX have chemical shift values at 6.15 τ, while the 6-methoxyl signals of the compounds in Table I appear upfield by 0.03∼0.05 p.p.m., and the 7-methoxyl groups, that are assumed to be more strongly shielded by diamagnetic anisotropy of the benzyl-benzene than 6-substituents, have higher τ values by 0.30∼0.34 p.p.m.. Furthermore, this shielding effect is to be seen in the chemical shift values of the aromatic protons of the isoquinoline moiety. In the spectrum of the compound (XIX), signals for protons of 5- and 8-positions at 3.47 τ appear as overlapped singlet, while I∼XII in Table I show two separated signals at 3.43∼3.50 τ and 3.65∼4.07 τ. The explanation for an upfield shift (by 0.18∼0.60 p.p.m.) of the latter signal may be given as the similar assumption applied above for the case of the methoxyls that the aromatic protons at 8-position are more strongly influenced by diamagnetic benzyl-benzene ring current than those at 5-position, deduces the assignment of upfield signals C(8)-protons. This assignment is evidenced to be correct by the fact that the spectrum of 1-(4-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline which has only one aromatic proton in its tetrahydroisoquinoline moiety at C(8)-position, has its signal at 4.12 τ. Further, the fact that the chemical shifts of C(5)-protons of compounds (I∼XII) have similar values of that of XIX, is explicable, as well as for the case of 6-methoxyl groups, as they are scarcely influenced by the benzyl-benzene ring current.

Summarizing the analyses stated above, a plausible three-dimensional picture representing the model conformation of the N-methylcoclaurine type compounds in deuteriochloroform solution at room temperature could be drawn approximately as shown in Fig. 1.

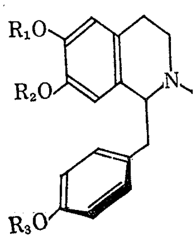


Fig 1.

However, a further inspection in Table I shows that protons at C(8)- of 7-hydroxy compounds (X and XII), have signals at about 0.3 p.p.m. lower than those of the 7-alkoxy compounds, and the methylimino signal of the former compounds appears higher by 0.1 p.p.m. than those of the latter compounds. And these higher values for methylimino protons are about the same for that of XIX, lacking a benzyl-benzene ring. Therefore, the methylimino groups of 7-hydroxy compounds are believed

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13) M. Tomita, T. Kikuchi, K. Bessho, Y. Inubushi: This Bulletin, 11, 1477 (1963).

to be free from the diamagnetic effect of benzyl-benzene anisotropy. On the other hand, τ values for C(8)-protons of 7-hydroxy compounds are still higher than those of XIX and XX, and the τ values for aromatic protons of XIX are not different from those of phenolic XX, make us assume that the upfield shift of C(8)-protons of X, XII, could be attributed to the diamagnetic anisotropy of the benzyl-benzene, though the effect is not so remarkable as for the case of 7-alkoxy compounds.

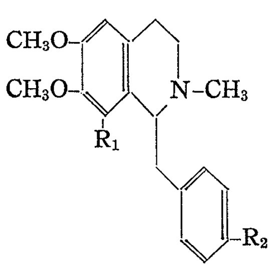
These circumstances could be interpreted by the assumption that the dihedral angles and relative locations between benzyl-benzene and isoquinoline rings are slightly different depending on the dimension of substituents at C(7), and consequently the influence of anisotropic effect on C(8)-protons appears differently in the spectra of 7-hydroxy compounds.

The consideration that substituents at C(7) have significant influence in spatial relative location of benzyl-benzene and isoquinoline rings in the molecule is fully evidenced by the analyses of the spectra of the compounds (XIII～XVIII) (Table II). Thus, compounds (XIV～XVIII), 7-substituted but lacking substituents at either 6- and/or 4′-positions, behave similarly as the compounds in Table I, and the substituents at C(6) and C(4′) should affect little to the relative location and dihedral angles between the rings in the molecule.

On the contrary, in compound (XIII) bearing no substituent at C(7), its two methoxyls have the same chemical shift values at 6.22 τ, and C(5)- and C(8)-protons appear both at 3.37 τ, nearly the same values for the aromatic protons of XIX and XX. Then, for the compounds having no 7-substituent, it is quite acceptable that C(8)-protons remain almost free from the anisotropic effect of the benzyl-benzene, and it follows that one of the conditions for the molecule to have a conformation drawn in Fig. 1, in other words, to detect the diamagnetic anisotropic effect of the benzyl-benzene of C(8)-protons, substituent of hydroxyl or alkoxyl group at C(7) is necessary.

From the foregoing arguments and molecular model examination, C(8)-substituted compounds (XXI～XXIII) are presumably unable to have an alike conformational state represented by Fig. 1. Their spectra measured are listed in Table IV. The high field signals of methoxyls (6.45～6.49 τ) always seen with the compounds in Tables I and II, do not appear in the case of C(8)-substituted compounds, and all the methoxyl

TABLE IV.



R₁	R₂		Aromatic-H	O-C$\underline{H}_3$			N-C$\underline{H}_3$
			C(5)-H	C(6)-, C(7)-	R₁	R₂	
O-Me	O-Me	XXI[14)]	3.63	6.15 6.18	6.05	6.23	7.65
Br	O-Me	XXII[*5]	3.37	6.14 (6H)		6.20	7.65
Br	OH	XXIII[15)]	3.35	6.14 (6H)			7.62

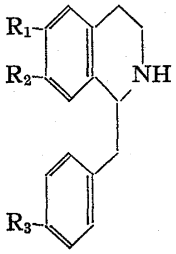
[*5] This sample was afforded from XXIII with ethereal diazomethane.

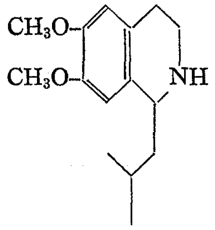
14) M. Tomita, K. Okui: Yakugaku Zasshi, **76**, 632 (1956).

15) K. Fujitani, T. Kishimoto, S. Niimura: *Ibid.*, **83**, 412 (1963).

groups have chemical shift values lower than 6.23 τ, and with the exception of 4′-methoxyl, they appear at almost same regions of those of XIX which have no benzyl-benzene in the molecule.

Table V.



R_1	R_2	R_3		Aromatic-H C(5)-, C(8)-H	O-C$\underline{H}_3$	N-$\underline{H}$
O-Me	O-Me	O-Me	XXIV[1]	3.37 3.42	6.17 6.20 6.22	7.97
O-Me	O-Me	H	XXV[12]	3.40	6.16 6.22	8.17
			XXVI[16]	3.42 (2H)	6.15 (6H)	8.20

As for methylimino proton signals, C(8)-substituted compounds show them at 7.62～7.65 τ; these values are higher than those of methylimino groups of the compounds in Table I, and even higher than that of XIX by about 0.1 p.p.m. These upfield shift of methylimino signals of C(8)-substituted compounds constitutes a confirmation of the assumption stated above, that a substituent at C(8)-position in the molecule has certain effect sterically on the conformational state of the benzyl-benzene ring, and reversely the benzyl-benzene is pushed forward to the methylimino side by the C(8)-substituent, and the effect of the diamagnetic anisotropy on the methylimino protons become positively detected.

Thus, the state represented by Fig. 1 is impossible for XXI～XXIII, but alternatively a possible state of their molecule may be drawn as Fig. 2.

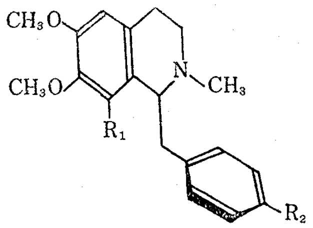


Fig. 2.

Conversely, the effect of the methylimino grouping on the conformational state of the benzyl-benzene ring should be revealed by the spectra of N-nor compounds (XXIV and XXV) (Table V). These compounds show their methoxyl signals at 6.16～6.22 τ, C(8)-protons at near 3.40 τ, and these values well coincide with those of XXVI which has no benzyl-benzene. These data show that the 7-methoxyl group or C(8)-protons of XXIV and XXV are not in the range of diamagnetic shielding effect of the ring at all. Thus, it is deduced that the presence of methylimino group has an effect on the benzyl-benzene ring, and the methylimino group is necessary together with above mentioned 7-alkoxy substitution to let the molecule assume the state drawn in Fig. 1.

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16) Unpublished.

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).