THE STRUCTURE OF THE ALKALOID MACARPINE

Narao Takao*, Miyoko Kamigauchi, Makiko Sugiura**, Ichiya Ninomiya, Okiko Miyata, and Takeaki Naito***
Pharmaceutical Chemistry** and Medicinal Chemistry*** Laboratories, Kobe Women's College of Pharmacy, Motoyamakita, Higashinada, Kobe 658, Japan.

Abstract The revised structure of the alkaloid macarpine (1c), which was isolated from both the plants and callus of Macleaya cordata, was proposed and unambiguously established by its total synthesis.

In 1955, Slavik et al[1,2] isolated a new fully aromatized benzo[c]phenanthridine alkaloid macarpine which has six oxygen functions from several papaveraceous plants and proposed[2] the tentative structure (1d) on the basis of the comparisons of mass and u.v. spectra with those of chelirubine and related alkaloids which have five oxygen functions. The structure of chelirubine was also proposed by Slavik[3] but later had to be revised to the structure (1b) by its total synthesis[4]. Recently, during the course of isolation experiment[5] of the alkaloids from the tissue cultures of Macleaya cordata by Takao's group, macarpine was isolated and the structural study using various spectral evidences revealed the necessity of revision of the proposed structure to (1c), which is now unambiguously established by its first total synthesis by Ninomiya's group.

(I) Isolation and Structure Elucidation of Macarpine (1c)**

During the course of biosynthetic study on the alkaloids from Macleaya cordata, an alkaloid (1c) was isolated from both this plant and callus cultures along with sanguinarine (1a) and chelirubine (1b) as their congeners[5].

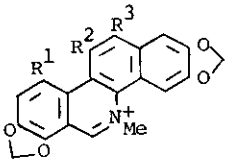
This alkaloid (1c) formed a crimson-red crystalline chloride, m.p. 283-285° , and was assigned as macarpine because of its close resemblance with the authentic sample[1,2] on their mass and u.v. spectra and m.p.'s though direct comparison was not available.[6] Macarpine (1c) was readily reduced with sodium borohydride to

the corresponding dihydro-base (2c), m.p. 178-179°, which had the molecular peak in its mass spectrum (M^+ 393.119) corresponding to the formula, $C_{22}H_{19}NO_6$.

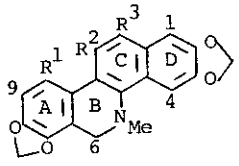
From the comparisons of n.m.r. spectra of dihydromacarpine (2c) and its congeners, dihydrosanguinarine (2a)[4,7] and dihydrochelirubine (2b)[4,7] as summarized in the table, the structure of macarpine (1c) was elucidated as follows.

Closely resembled n.m.r. spectra of (2c) and dihydrosanguinarine (2a) first located two methylenedioxy groups in the 2,3- and 7,8-positions in macarpine. Then, comparison with dihydrochelirubine (2b) revealed the location of one methoxy group at C-10 in the ring A. Finally, thorough analysis of the n.m.r. peaks of (2c) could assign the location of the last methoxy group as at C-12, thus offered the structure of macarpine (1c) as proposed by the formula (1c).

This proposal was further assured by the observation of the n.O.e. values between 12-OMe (irradiated) and 1-H (observed), 12-OMe and 11-H, 10-OMe and 11-H, and 10-OMe and 9-H, as 16, 47, 13, and 48 % respectively.



(1a,b,c, and d)



(2a,b, and c)

	R^1	R^2	R^3			
1a	H	H	H	Sanguinarine	2a	Dihydrosanguinarine
1b	OMe	H	H	Chelirubine	2b	Dihydrochelirubine
1c	OMe	H	OMe	Macarpine (Ours)	2c	Dihydromacarpine
1d	H	OMe	OMe	(Slavik's Formula)[2]		

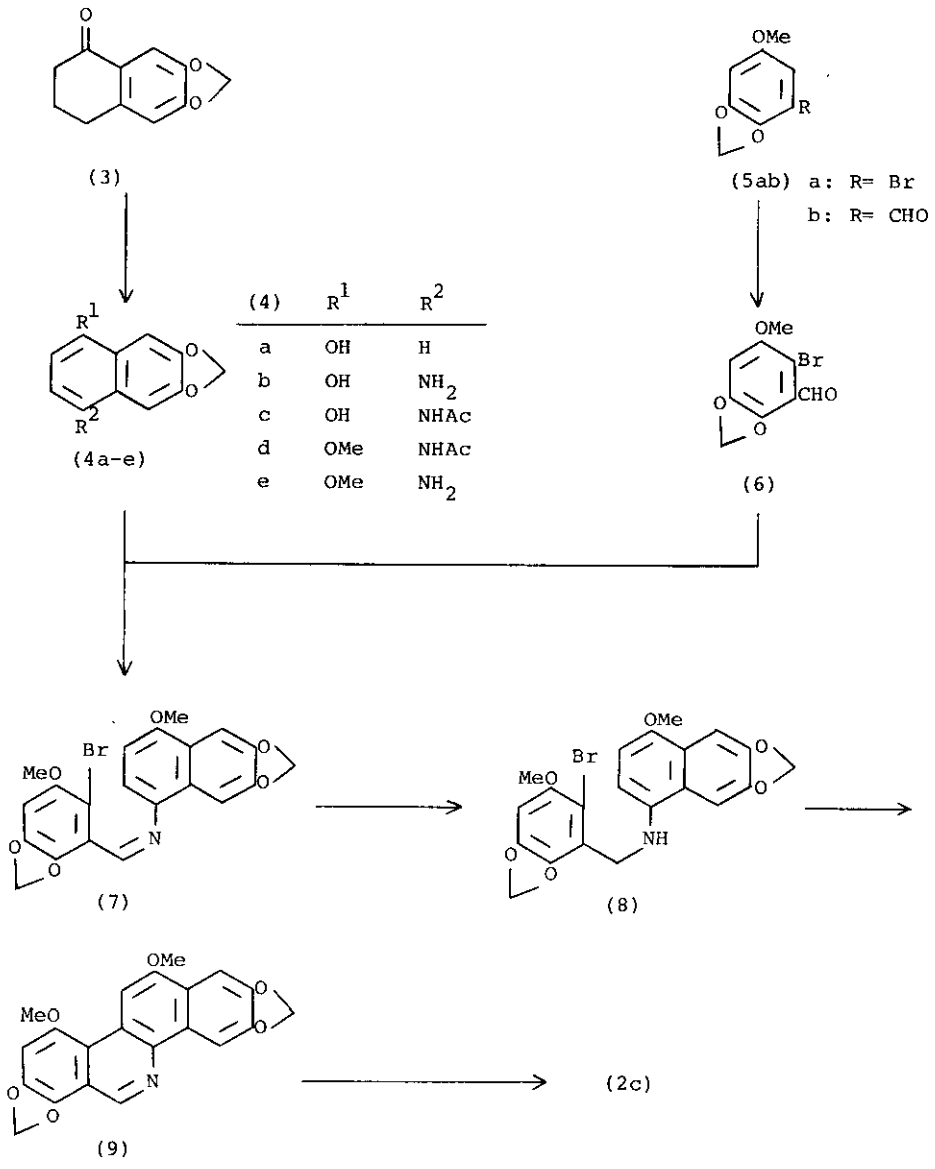
TABLE δ ($CDCl_3$)

	(2a)[4,7]	(2b)[4,7]	(2c)
1-H	7.10	7.11	7.57
4-H	7.72	7.72	7.71
N-Me	2.54	2.54	2.53
6-H_2	4.14	4.07	4.11
9-H	6.83 (d, J=8Hz)	6.59	6.64
10-OMe	(10-H 7.30 (d, J=8Hz))	3.81	3.89
11-H	7.69 (d, J=9Hz)	8.35 (d, J=9Hz)	7.87
12-OMe	(12-H 7.46 (d, J=9Hz))	(12-H 7.47 (d, J=9Hz))	4.00

(II) Total Synthesis of Macarpine (1c)***

The above elucidation of the structure of macarpine (1c) was unambiguously established by the following total synthesis, which was virtually followed by the route described by Kessar et al.[8] as shown in the scheme.

For the synthesis of dihydromacarpine (2c), 1-amino-4-methoxy-6,7-methylenedioxynaphthalene (4e) and 2-bromo-3-methoxy-5,6-methylenedioxybenzaldehyde (6) were prepared as follows.



SCHEME

α-Bromination of 6,7-methylenedioxy-1-tetralone (3)[9] with bromine under usual manner and successive dehydrobromination of the 1-bromoketone with lithium carbonate in the presence of lithium bromide gave the 1-naphthol (4a). Following the procedure described by Bachman et al[10], the 1-naphthol (4a) was converted into the corresponding naphthylamine (4e), m.p. 142.5-144°, in five steps of reactions including diazo-coupling, reduction, acetylation, methylation, and hydrolysis in overall yield of 25 %.

As of the other half of the condensation, the bromoaldehyde (6) was prepared as follows. Treatment of the Grignard reagent from the bromide (5a)[4] with dimethylformamide gave the aldehyde (5b) in 92 % yield, which was then brominated in the presence of iron[11] to afford the bromoaldehyde (6), m.p. 182-183.5°.

The Schiff's base (7), which was prepared from the naphthylamine (4e) and bromoaldehyde (6), was reduced with excessive amount of sodium borohydride to give the corresponding amine (8) in 54 % yield, m.p. 169-170°, ν_{max} 3400 cm^{-1}, δ 4.50 (2H, s, $ArCH_2N$).

Irradiation of a 0.001 M solution of the bromoamine (8) in acetonitrile-water (9 : 1) containing 0.002 M sodium hydroxide with a high pressure mercury lamp (with pyrex filter) at room temperature in a nitrogen stream for 2 h. afforded the phenanthridine (9) in 42 % yield, m.p.278-282°(dec), δ 9.25 (1H, s, 6-H), 8.75 and 8.68 (each 1H, s, 4- and 11-H), 7.65 and 7.03 (each 1H, s, 1- and 9-H), 6.22 (2H, s, OCH_2O), 6.11 (2H, s, OCH_2O), 4.14 (3H, s, OMe), and 4.09 (3H, s, OMe).

Reductive alkylation of the phenanthridine (9) with sodium borohydride in formic acid [12] furnished the N-methylamine (2c) in 53 % yield, m.p. 178-179° , which was identical with dihydromacarpine, prepared from natural macarpine , upon direct comparisons (mixed m.p., Rf values on t.l.c., i.r. and n.m.r. spectra), thus unambiguously established the structure of the alkaloid macarpine as proposed in this paper.

ACKNOWLEDGEMENT

This work was in part supported by a Grant-in-Aid to I.N. by the Ministry of Education, Science and Culture (Japan). The authors (N.T.) are also grateful to Dr. H. Fujiwara, Faculty of Pharmaceutical Sciences, Osaka University, for his advice on the n.O.e. measurement.

REFERENCES

1a) J. Slavik and L. Slavikova, Coll. Czech. Chem. Commun., 1955, 20, 356.

b) J. Slavik, L. Slavikova, and J. Appelt, Coll. Czech. Chem. Commun., 1965, 30, 887.

c) L. Slavikova and J. Slavik, Coll. Czech. Chem. Commun., 1966, 31, 3362.

2 J. Slavik, L. Slavikova, and K. Haisova, Coll. Czech. Chem. Commun., 1967, 32, 4420.

3 J. Slavik, L. Dolejs, V. Hanus, and A. D. Cross, Coll. Czech. Chem. Commun., 1968, 33, 1619.

4a) H. Ishii, K. Harada, T. Ishida, E. Ueda, K. Nakajima, I. Ninomiya, T. Naito, and T. Kiguchi, Tetrahedron Letters, 1975, 319.

b) H. Ishii, E. Ueda, K. Nakajima, T. Ishida, T. Ishikawa, K. Harada, I. Ninomiya, T. Naito, and T. Kiguchi, Chem. Pharm. Bull. (Japan), 1978, 26, 864.

5 Details of the derivation and formation of the callus from Macleaya cordata will be described elsewhere (N.T.).

6 A sample of the alkaloid has not been obtained upon request.

7 M. Onda, K. Abe, K. Yonezawa, N. Esumi, and T. Suzuki, Chem. Pharm. Bull. (Japan), 1970, 18, 1435.

8 S. V. Kessar, Y. P. Gupta, K. Dhingra, G. S. Sharma, and S. Narula, Tetrahedron Letters, 1977, 1459.

9 I. Ninomiya, T. Naito, H. Ishii, T. Ishida, M. Ueda, and K. Harada, J. Chem. Soc. Perkin I, 1975, 762.

10 G. B. Bachman and J. W. Wetzel, J. Org. Chem., 1946, 11, 454.

11 T. Kametani, T. Honda, H. Inoue, and K. Fukumoto, J. Chem. Soc. Perkin I, 1976, 1221.

12 H. Ishii, T. Deushi, K. Harada, M. Sakamoto, K. Watanabe, E. Ueda, T. Ishida, and T. Ishikawa, Abstr. Papers, 9th. Congress of Heterocyclic Chemistry, Fukuoka, Japan, 1976, p 136.

Received, 11th October, 1980