

THE STRUCTURE OF THE ALKALOID MACARPINE

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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 proposed² 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 Slavik³ but later had to be revised to the structure (1b) by its total synthesis⁴. Recently, during the course of isolation experiment⁵ 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 congeners⁵.

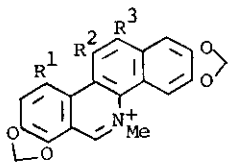
This alkaloid (1c) formed a crimson-red crystalline chloride, m.p. 283-285°, and was assigned as macarpine because of its close resemblance with the authentic sample^{1,2} on their mass and u.v. spectra and m.p.'s though direct comparison was not available.⁶ Macarpine (1c) was readily reduced with sodium 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, $C_{22}H_{19}NO_6$.

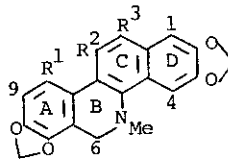
From the comparisons of n.m.r. spectra of dihydromacarpine (2c) and its congeners, dihydrosanguinarine (2a)^{4,7} and dihydrochelirubine (2b)^{4,7} as summarized in the table, the structure of macarpine (1c) was elucidated as follows.

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)

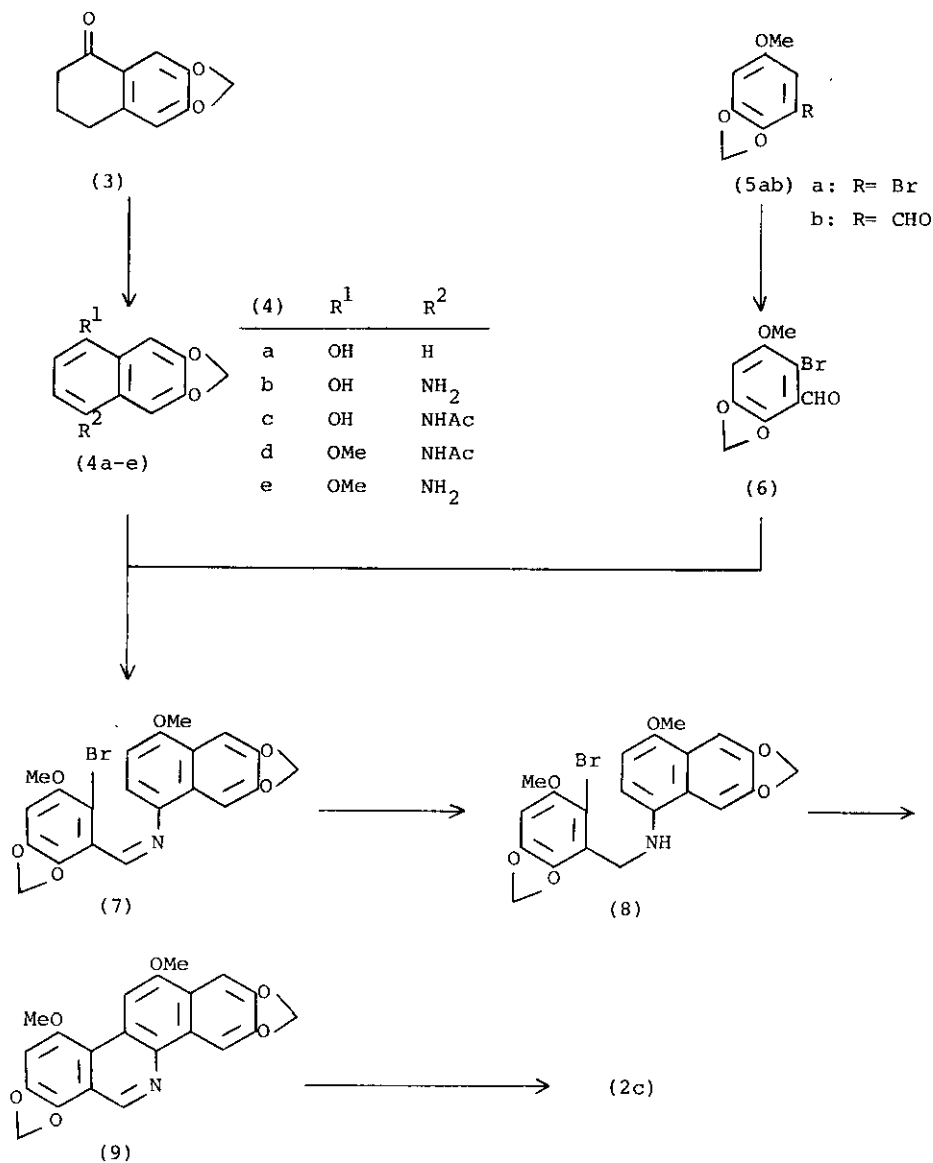
	R ¹	R ²	R ³		
1a	H	H	H	Sanguinarine	2a Dihydrosanguinarine
1b	OMe	H	H	Chelirubine	2b Dihydrochelirubine
1c	OMe	H	OMe	Macarpine (Ours)	2c Dihydromacarpine
1d	H	OMe	OMe	(Slavik's Formula) ²	

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-methylenedioxy-naphthalene (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 iron¹¹ 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 acid¹² 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.

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