AN EFFICIENT METHOD FOR C_8-N BOND CLEAVAGE OF TETRAHYDROPROTOBERBERINES USING ETHYL CHLOROFORMATE

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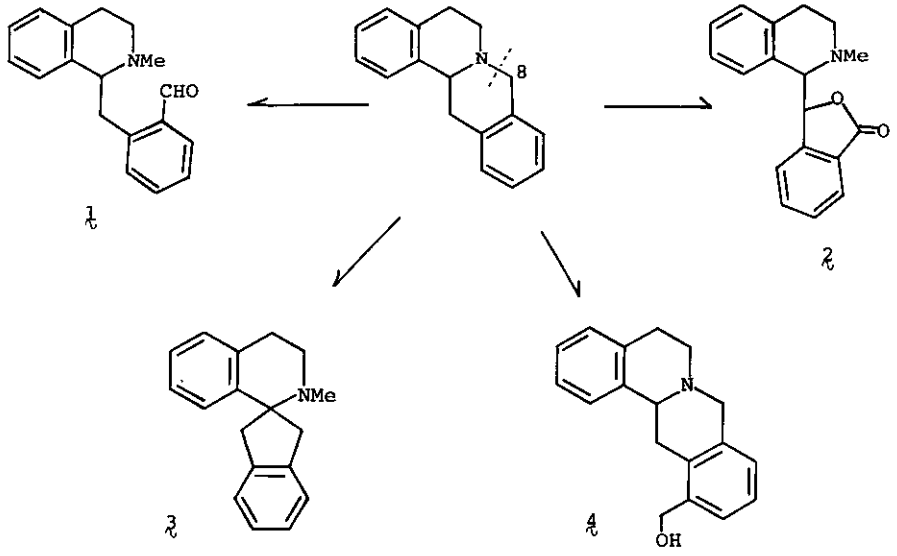
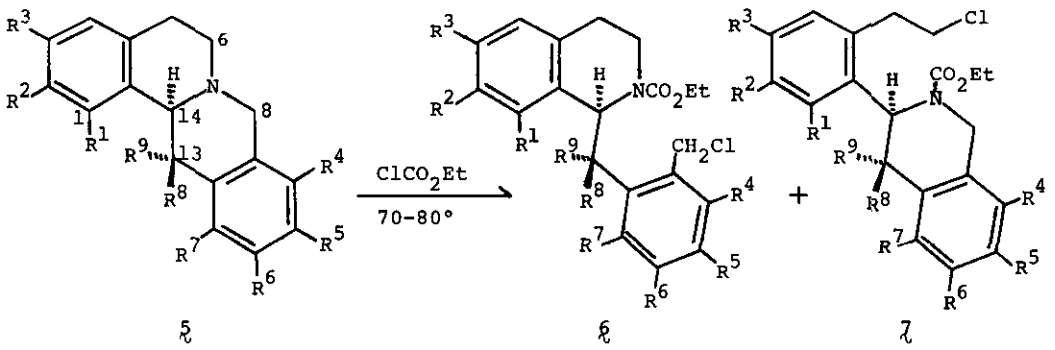
Abstract —— Ethyl chloroformate was found to be an effective reagent for C_8-N bond cleavage of tetrahydroprotoberberines having a *trans*-quinolizidine conformation. And some tetrahydroprotoberberines having a *cis*-conformation resulted in exclusive C_6-N bond cleavage on treatment with this reagent.

Regioselective C_8-N bond cleavage of tetrahydroprotoberberines might be a requisite key-step in their conversions into the related alkaloids, e.g. secoberbines (1), phthalideisoquinolines (2), spirobenzylisoquinolines (3), and retroprotoberberines (4). Although many methods for C-N bond cleavage of tetrahydroproto-



berberine system have so far been reported, little is known concerning regioselective and general C_8-N bond cleavage.[1] Now we wish to describe in this communication a regioselective and general method for C_8-N bond cleavage of tetrahydroprotoberberine system using ethyl chloroformate.[2]

A variety of tetrahydroprotoberberines (5a-k) were treated with large excess of ethyl chloroformate (*ca.* 30 ml per 1 g of 5) at 70-80°C for 3.5-108 hr to give a mixture of the C-N bond cleavage product (6 and/or 7) and the unchanged starting material, which was separated by column chromatography or preparative thin layer chromatography. Structures of the products (6 and 7) were confirmed by chemical



5 6 7

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
a	H	OCH_2O		OMe	OMe	H	H	H	H
b	*H*	*OCH_2O*		*OMe*	*OMe*	*H*	*H*	*OAc*	*H*
c	H	OCH_2O		OMe	OMe	H	H	H	OAc
d	H	OMe	OMe	OCH_2O		H	H	H	H
e	H	OMe	OMe	H	OCH_2O		H	H	H
f	H	OMe	OMe	H	H	OCH_2O		H	H
g	H	OMe	OMe	H	OMe	OMe	H	H	H
h	H	OCH_2O		OMe	OMe	H	H	H	OCOPh
i	H	OMe	OMe	H	OMe	OMe	H	H	Me
j	OMe	OMe	OMe	H	OCH_2O		H	H	H
k	H	OCH_2O		H	H	H	H	H	H

and physical evidences. The experimental results were summarized in Table I. Exclusive C_8-N bond cleavage took place in the cases of 5a, 5b, 5d, 5e, 5f, and 5g, while selective C_6-N bond fission was observed in the case of 5j. Other

Table I. Reaction of Tetrahydroprotoberberines (5) with Ethyl Chloroformate

Entry	Substrate	Temp. (°C)	Time (hr)	Yields (%) of Products		
				6	7	Recovery of 5
1	5a	80	6	61	0	24
2	5b	70	72	46	0	54
3	5c	70	108	37	30	22
4	5d	70	40	31	0	56
5	5e	80	3.5	81	0	0
6	5f	70	48	41	0	36
7	5g	70	24	82	0	9
8	5h	80	6.5	37	22	24
9	5i	80	48	4	64	5
10	5j	70	20	0	39	33
11	5k	80	28	0	0	100

substrates (5c, 5h, and 5i) gave the regioisomeric mixture (6 and 7) and compound 5k was recovered unchanged completely even after 28 hr heating.

Based on the above results, the following characteristics of this reaction can be summarized.

a) Generally regioselective C_8-N bond cleavage took place regardless of the substitution pattern on ring D (entry 1, 2, 4, 5, 6, 7), but the presence of the electron-donating group in ring D would be a necessity to this reaction (entry 11).

b) The above regioselectivity was affected by the substituent at C_1 or C_{13}-eq (entry 3, 8, 9, 10).

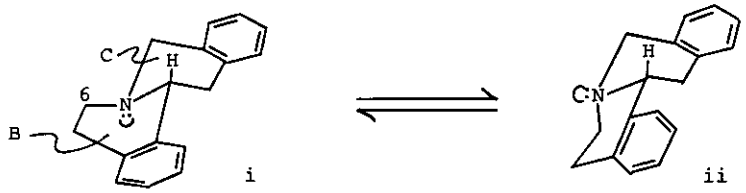
c) No C_{14}-N bond cleavage was observed presumably due to the severe steric hindrance at C_{14}.

As the introduction of the substituent at C_1 or C_{13} in tetrahydroprotoberberine has been shown to change its B/C ring conformation, the B/C ring conformation is anticipated to be an important factor in regulating the regioselectivity of this reaction. Kametani *et al.* have established the conformations of various tetrahydroprotoberberines by their ^{13}C-NMR spectra, indicating that C_6 of *trans* isomer (i) appears at *ca.* 51.4 ppm and that of *cis* isomer (ii) at lower field than 57.0 ppm.[3] In Table II were summarized the C_6 chemical shifts of 5a-k and the ratios

of the conformations (i:ii) in the equilibrium (i⇌ii) calculated on the basis of the assumption that 51.4 ppm is the value for i and 46.4 ppm for ii.

Table II. The Relation Between the Conformational Ratio (i:ii) and the Products Ratio (6:7)

Compound	C_6 Chemical Shift(δ)	i : ii	6 : 7
5a	51.3	100: 0	100: 0
5b	51.4	100: 0	100: 0
5c	49.1	55: 45	55: 45
5d	51.3	100: 0	100: 0
5e	51.3	100: 0	100: 0
5f	51.3	100: 0	100: 0
5g	51.4	100: 0	100: 0
5h	49.4	60: 40	63: 37
5i	47.4	20: 80	6: 94
5j	46.4	0:100	0:100
5k	51.2	100: 0	—



Of all entries, the ratios of the regioselectivity (6:7) are found to be in fair agreement with those of the conformer (i:ii), indicating that tetrahydroprotoberberines having the *trans* conformer (i) give the C_8-N bond cleavage products predominantly. The present reaction provides a general method for the selective C_8-N bond cleavage of a number of tetrahydroprotoberberines.

Recently, the conversions of tetrahydroprotoberberines into (±)-canadaline, a secoberbine alkaloid, and (±)-α- and (±)-β-hydrastine, phthalideisoquinoline alkaloids, have successfully been achieved by this C_8-N bond cleavage method.[4,5]

REFERENCES AND NOTES

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