ORGANIC AND BIOLOGICAL ASPECTS OF BERBERINE ALKALOIDS*

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Recent chemical and biological progresses of berberine alkaloids have been reviewed.

I Introduction

Berberine alkaloids are widely distributed in numerous plants of Berberidaceae, Menispermaceae, Ranunculaceae and Rutaceae. Since berberine, a typical representative of these alkaloids, has been isolated first in 1926, several thousand publications on chemical and pharmacological studies of the berberine alkaloids were reported.[1] During the past decade or so, there are salient development in both area. I would like to describe a brief account of recent chemical and biological progresses of berberine alkaloids.

II Organic chemistry

1 Synthesis of protoberberine alkaloids by photochemistry

Recently, photochemistry serves an excellent method for synthesis of protoberberine alkaloids.

Irradiation of *cis*-1-benzylidene-2-carbethoxy-1,2,3,4-tetrahydroisoquinoline 1 gave *N*-carbethoxydehydroaporphane 3 and 8-oxodehydroprotoberberine 4 in 65% and 10-21% yields, respectively[2] (Scheme 1). Cyclization to 4 apparently proceedes *via* a cis-trans isomerzation, and yield depends upon the reaction conditions. Irradiation of benzylidene derivatives (5 and 6),[3,4] *trans*-analogs

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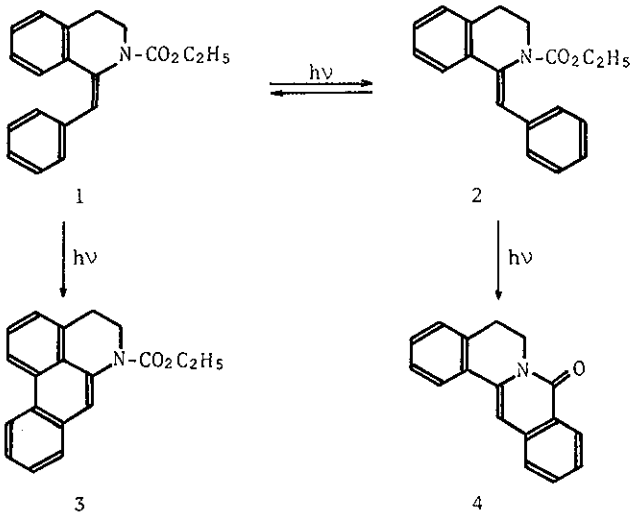
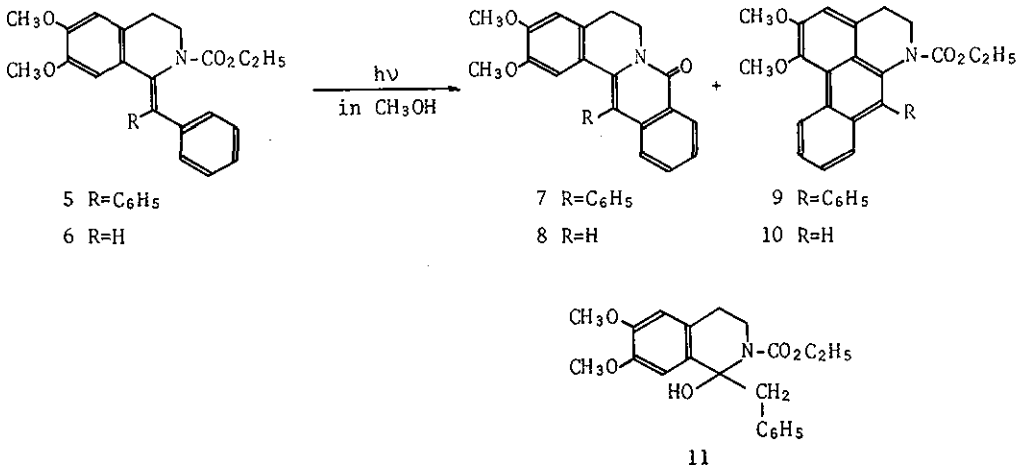
* Dedicated to Professor Dr. Tsunematsu Takemoto on the occasion of his retirement.

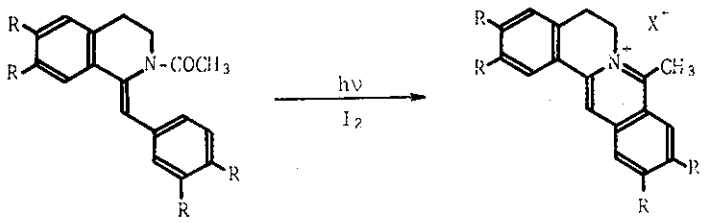


Scheme 1

of 1, actually gave 8-oxodehydroprotoberberines (7 and 8) (60-64%) as the major product, respectively, in addition to *N*-carbethoxy-6a,7-dehydronornuciferines (9 and 10) and 1-benzyl-2-carbethoxy-1,2,3,4-tetrahydro-1-hydroxy-6,7-dimethoxy-isoquinoline 11[4] (Scheme 2). It is of interest that when irradiation of 5 was carried out in the presence of iodine, 9 was obtained as the major product (60%). In this photolysis, 8-oxodehydroprotoberberine 7 was obtained only in 9% yield.



Scheme 2



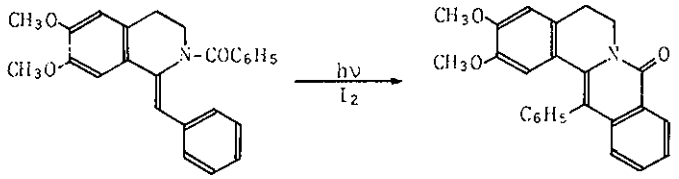
12 R=H
13 R=OCH_3

14 R=H
15 R=OCH_3

Scheme 3

Although the starting materials, 1-benzyl derivatives, are accessible from 1-benzyl-1,2,3,4-tetrahydroisoquinolines, the yields are not satisfactory.

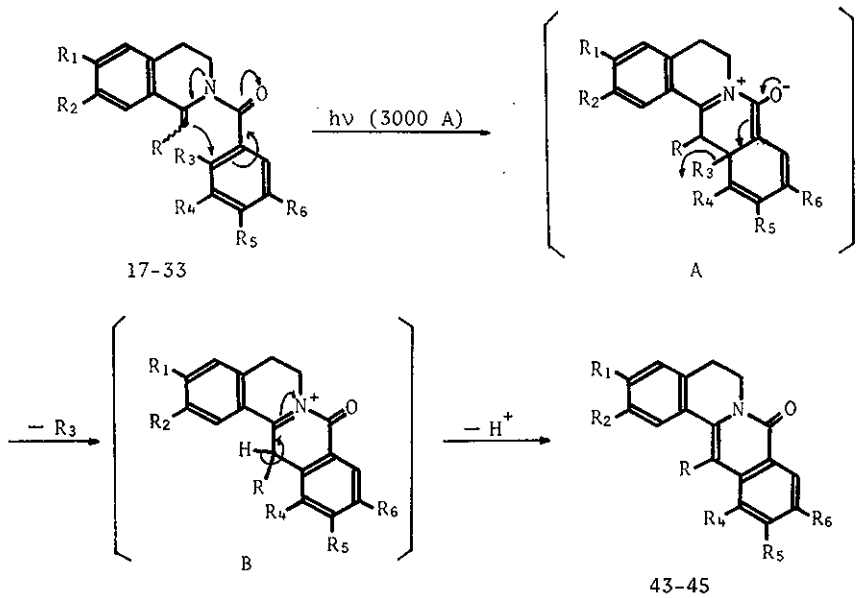
In a related study, 2-acetyl-1-benzylidene-1,2,3,4-tetrahydroisoquinoline 12 and 2-acetyl-1-(3,4-dimethoxybenzylidene)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline 13 in methanol with an equimolar amount of iodine gave 8-methyldehydroberbinium iodide 14 and dehydrocoralydinium iodide 15 in moderate yields, respectively[5] (Scheme 3). A similar class of compound, *trans*-1-benzylidene-2-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 16 underwent different photocyclization. Irradiation of 16 in the presence of iodine and cupric acetate afforded 7 in 50% yield[3] (Scheme 4).



16 7

Scheme 4

In connection with new routes to protoberberine alkaloids, photocyclizations of the 2-aroyl enamides have been explored.[4,6-8] While irradiation of enamides 17-26 having no substituent at *ortho*-position with a medium pressure mercury lamp gave 8-oxotetrahydroprotoberberines 34-42, irradiation of *ortho*-substituted



Scheme 5

2-aroyl-1-methylene 27-32 or ethylene enamides 33 gave unexpected 8-oxoprotoberberines 43-45 under the elimination of *ortho*-substituent in good yields (Scheme 5). The results are collected in Table I.

A proposed mechanism[4,8] for the photocyclization of the enamides involves analogy of a hexatriene-cyclohexadiene isomerisation.[9] Thus, the formed azacyclohexadiene intermediate A loses the *ortho*-substituent by electron-redistribution followed by elimination of 13-proton to form 8-oxoprotoberberine (Scheme 5). The unsubstituted enamides gave an analogous intermediate which allows a 1,5-hydrogen shift to give 8-oxoberbines (Scheme 6). This procedure provides a convenient synthetic route of protoberberine derivatives. Another advantage is that the starting enamides are readily prepared by treating the 1-methyl(ethyl)isoquinoline with the appropriate aroyl anhydride in high yields.

The protopine alkaloids 45-47 which possess transannular carbonyl and tertiary amine functions in a ten-membered ring were converted to berberine alkaloids 48-50 on irradiation[10] (Scheme 7). An increase of yield was observed

Table I

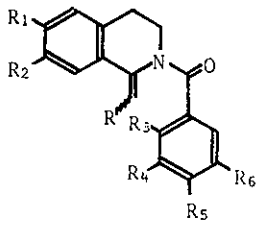
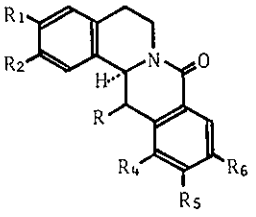
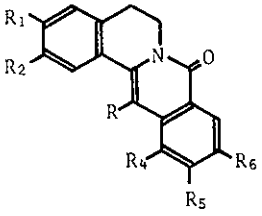
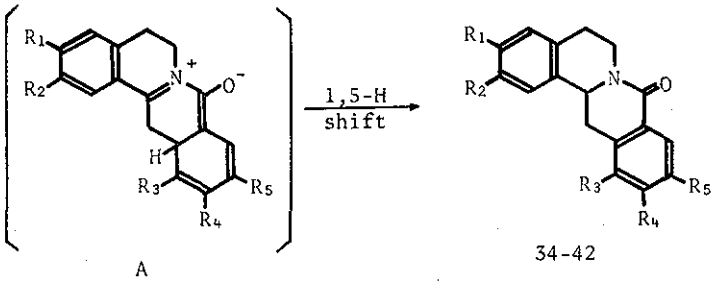
Starting enamide	Product(s)		Ref
	 Yield	 Yield	
17 $R=R_1=R_2=R_3=R_4=R_5=R_6=H$	34 $R=R_1=R_2=R_4=R_5=R_6=H$ ca 70%		7
18 $R_1=R_2=R_3=R_4=R_5=R_6=H$, $R=CH_3$	35 $R_1=R_2=R_4=R_5=R_6=H$, $R=CH_3$ ca 70%		7
19 $R=R_3=R_4=H$, $R_1=R_2=R_5=$ $R_6=OCH_3$	36 $R=R_4=H$, $R_1=R_2=R_5=R_6=$ OCH_3 5% (ref 7), 93.5% (ref 9)	43 $R=R_4=H$, $R_1=R_2=R_5=R_6=$ OCH_3 40% (ref 7)	7 9
20 $R=R_3=H$, $R_1=R_2=R_4=R_5=$ $R_6=OCH_3$	37 $R=H$, $R_1=R_2=R_4=R_5=R_6=$ OCH_3 70%		8 9
21 $R=R_3=R_4=R_5=R_6=H$, $R_1=$ $R_2=OCH_3$	38 $R=R_4=R_5=R_6=H$, $R_1=R_2=$ OCH_3 96.7%		9
22 $R=R_3=R_4=H$, $R_1=R_2=OCH_3$, $R_5+R_6=OCH_2O$	39 $R=R_4=H$, $R_1=R_2=OCH_3$, $R_5+R_6=OCH_2O$ 75%		9
23 $R=R_3=R_4=H$, $R_1=R_2=R_5=$ $R_6=OCH_3$	36		9

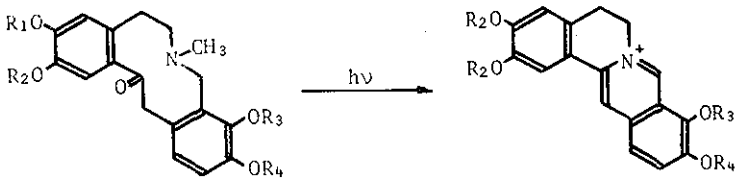
Table I (continued)

Starting enamide	Product(s)		Ref
24 $R=R_3=R_4=R_6=H$, $R_1=R_2=OCH_3$, $R_5=CH_3$	40 $R=R_4=R_6=H$, $R_1=R_2=OCH_3$ $R_5=CH_3$ 85%		9
25 $R=R_3=R_4=R_6=H$, $R_1=R_2=OCH_3$, $R_5=Cl$	41 $R=R_4=R_6=H$, $R_1=R_2=OCH_3$, $R_5=Cl$ 76%		9
26 $R=R_3=R_4=R_6=H$, $R_1=R_2=OCH_3$, $R_5=C_6H_5$	42 $R=R_4=R_6=H$, $R_1=R_2=OCH_3$, $R_5=C_6H_5$ 76%		9
27 $R=R_4=R_5=R_6=H$, $R_1=R_2=OCH_3$, $R_3=OAc$		44 $R=R_4=R_5=R_6=H$, $R_1=R_2=OCH_3$ 76%	8 5
28 $R=R_5=R_6=H$, $R_1=R_2=OCH_3$		45 $R=R_5=R_6=H$, $R_1=R_2=R_4=OCH_3$ 85%	8 5
29 $R=R_4=R_5=R_6=H$, $R_1=R_2=OCH_3$, $R_3=X$ (Cl or Br)		44 50%	8 5
29 X=F		44 85%	5
30 $R=R_4=R_5=R_6=H$, $R_1=R_2=OCH_3$, $R_3=NO_2$		44 17%	8 5
31 $R=R_4=H$, $R_1=R_2=R_3=R_5=R_6=OCH_3$		43 85%	5
32 $R=R_4=R_5=R_6=H$, $R_1=R_2=OCH_3$, $R_3=SCH_3$		44 55%	5
33 $R_4=H$, $R=CH_3$, $R_1=R_2=R_3=OCH_3$		45 $R_4=H$, $R=CH_3$, $R_1=R_2=R_5=R_6=OCH_3$ 69%	5



A 34-42

Scheme 6



45 $R_1=R_2=CH_3$, $R_3+R_4=CH_2$
46 $R_1+R_2=R_3+R_4=CH_2$
47 $R_1+R_2=CH_2$, $R_3=R_4=CH_3$

48 $R_1=R_2=CH_3$, $R_3+R_4=CH_2$
49 $R_1+R_2=R_3+R_4=CH_2$
50 $R_1+R_2=CH_2$, $R_3=R_4=CH_3$

Scheme 7

upon irradiation of α-allocryptopine in chloroform, in which a 76% of berberine (as nitrate) was isolated. Apparently the reaction proceeds *via* a radical intermediate, couple with the fact that chloroform was known to be good radical source with the aid of irradiation (Table II).

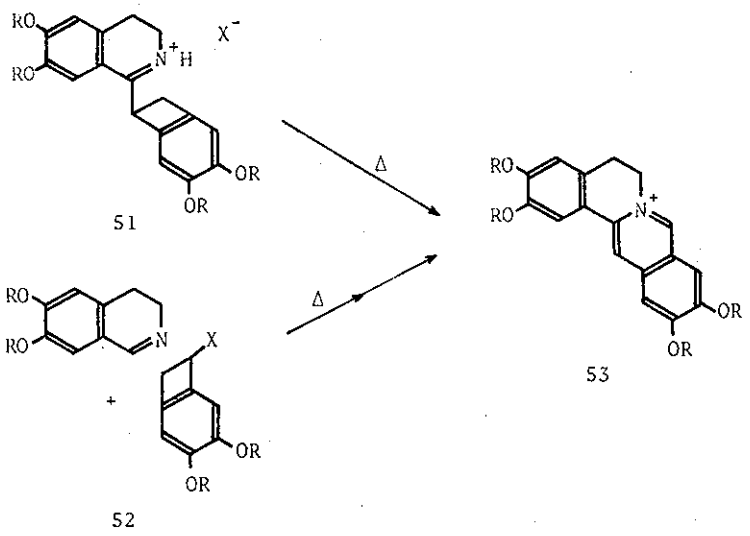
Table II

Irradiation for 100 hr in 95% EtOH			Yields
Cryptopine 45	→	Epiberberine 48	34%
Protopine 46	→	Coptisine 49	23%
α-Allocryptopine 47	→	Berberine 50	76%*

*in $CHCl_3$

2 Synthesis of protoberberine alkaloids by thermolysis

The fact that the benzocyclobutenes are open to give the *o*-qinodimethane intermediate during the first stage of thermolysis was proven by the condensation with the dienophiles[11] and was extended to clever synthetic method of the isoquinoline alkaloids.[12] For instance, the starting benzocyclobutene 51 and 52 were subjected to thermolysis to give the protoberberine 53 in good yield (Scheme 8). The extensive application to synthesis of protoberberine alkaloids was reviewed by Kametani et al.[12,13]

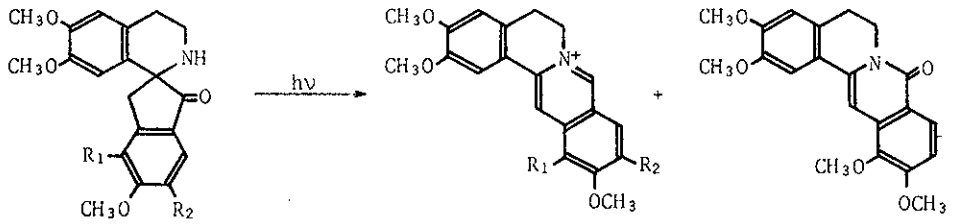


Scheme 8

3 Protoberberine ⇄ spirobenzylisoquinoline rearrangement

Research in the protoberberine ⇄ spirobenzylisoquinoline rearrangement has contributed to supply the new route to respect alkaloids.

Photorearrangement ($n\rightarrow\pi^*$) of the ketospiroisoquinoline 54 in tetrahydrofuran gave berberinium derivative 56 and lactame 58 in 80% and 20% yields, respectively.[14,15] Analogously 55 gave dehydroxylopinine 57[14] (Scheme 9). The yields are sufficiently high so that the rearrangement may serve as a synthetic method.



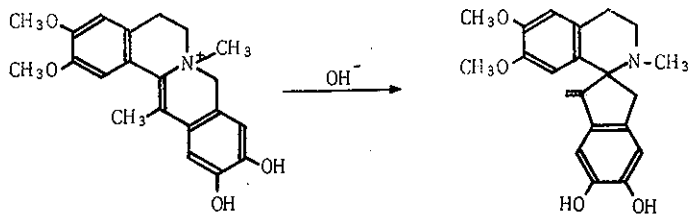
54 R_1=OCH_3, R_2=H
55 R_1=H, R_2=OCH_3

56 R_1=OCH_3, R_2=H
57 R_1=H, R_2=OCH_3

58

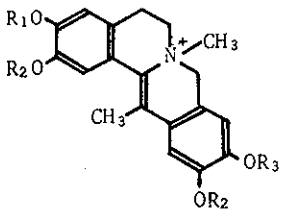
Scheme 9

In connection with this reaction, the rearrangement of the protoberberines to the spirobenzylisoquinoline alkaloids has aroused interest. The first example of the rearrangement of the protoberberine to an ochotensine type alkaloid was observed on treatment of 2,3-dimethoxy-10,11-dihydroxy-13-methyl-7,8-dihydroprotoberberine methobromide 59 with alkali[16] (Scheme 10). Analogous rearrangement in phenolic dihydroprotoberberine methobromides 61-63 has been demonstrated.[17,18] Of interest was noted that 3-hydroxy-2,10,11-trimethoxy-13-methyl-7,8-dihydroprotoberberine methobromide 64, when treated with base, gave 5,6,7,7a-tetrahydro-

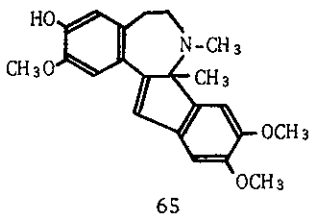


59 60

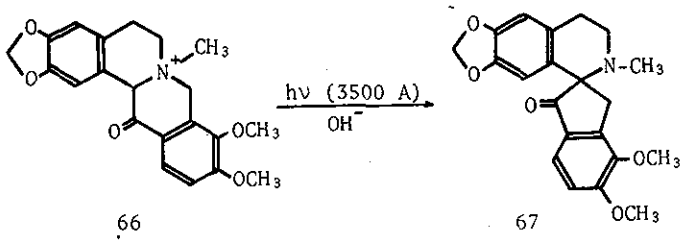
Scheme 10



61 R_1=R_3=H, R_2=CH_3
62 R_2=H, R_1=R_3=CH_3
63 R_3=H, R_1=R_2=CH_3
64 R_1=H, R_2=R_3=CH_3



65



66 67

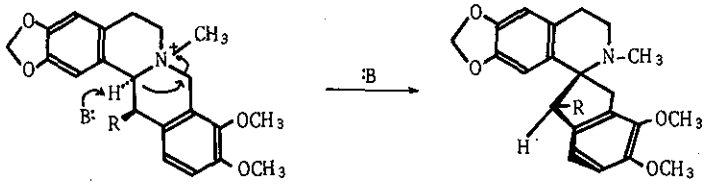
Scheme 11

2,9,10-trimethoxy-7,7a-dimethylbenz[a]indeno[1,2-6]azepin-3-ol 65[18] in 41% yield instead of the spirobenzylisoquinoline.

13-Ketocanadine methylmethosulfate 66, whereas it is stable for alkali, undergoes similar rearrangement to 1,2,3,4-tetrahydro-6,7-methylenedioxy-4′,5′-dimethoxy-1-spiro-2′-indan-1′-one 67 in 45% yield on irradiation[19] (Scheme 11).

Since these rearrangements involve an o-qinodimethine as the general intermediate, it seems to be inadequate as the synthetic strategy for the optically active spirobenzylisoquinolines.

Recently, anionic rearrangement of the non-phenolic protoberberine methosalts was reported.[20-22] Treatment of *l*-(14 S)-β- 68a and *d*-(14 R)-β-canadine methochloride 68b with an organometalic reagent in tetrahydrofuran, afforded *d*- 70a and *l*-2,3-methylenedioxy-9,10-dimethoxyochotensanes 70b, respectively (Scheme 12). Yields are shown in Table III.[22] Analogously, thalictricavine methochloride 69 gave 2,3-methylenedioxy-9,10-dimethoxy-13-methylochotensane 71 together with the usual Hofmann methine[22] (Scheme 12).



68a R=H, 14 S
b R=H, 14 R
69 R=CH3

70a R=H, 14 R
b R=H, 14 S
71 R=CH3

Scheme 12

Table III

	n-BuLi	C_6H_5Li	$NaCH_2SOCH_3$	$LiAlH_4$	Na/Hg
I	—	—	29.1%	62.4%	—
Cl	54.5%	—	63.3%	—	3.5%
CH_3OSO_3	—	25.0%	—	60.0%	—

III Biological activity

1 Antimicrobial activity

Berberine alkaloids have a number of biological activities. Since berberine-containing plants have been used for more than 2000 years in traditional folk medicine for therapeutic treatment[23], it is not surprising that berberine alkaloids possess antimicrobial activity against wide variety microorganisms including fungi and protozoa. Numerous publications on the antibacterial effects of berberine have been summarized previously by Hahn and Ciak.[24]

The first systematic study on antibacterial activities of berberine chloride, iodide and palmatine iodide against Vibrio, Eberthella, Salmonella and Escherichia organisms has been reported by Soda.[25] He found that the antibacterial action of berberine chloride was virtually invariant over ranges of pH 5-9 of the medium. The more extensive screening studies have been published by several authors.[26,27] Table IV are cited from the paper of Amin et al.[27]

Phellodendron amurense (Rutaceae), a typical berberine-containing plant, has been once used as a folkloric antidysenteric[28] in Japan, which can be ascribed unambiguously to berberine alkaloids. Another berberine-containing plant, *Berberis aristata* (Berberidaceae) was used as the chemotherapy for all cases of cholera and other bacterial diarrhoeas[29,30] in the same manner as chloramphenicol. The modes of action of berberine were shown that the cell-free

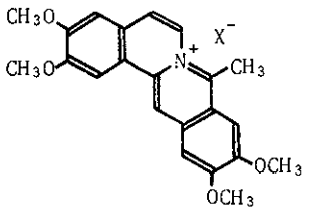
Table IV Antimicrobial Activity of Berberine Sulfate

Organism	Minimal growth inhibitory concentration, μg/ml
Bacillus pumilus	25.0
B. cereus	50.0
B. sublilis	25.0
Corynebacterium diphtheriae	6.2
Escherichia coli	50.0 — >100.0
Klebsiella pneumoniae	25.0
Pseudomonas pyocyanea	>100.0
P. fluorescens	>100.0
Salmonella paratyphi	>100.0
S. schottmuelleri	>100.0
S. typhimurium	>100.0
S. typhi	>100.0
Shigella boydii	12.5
Staphylococcus aureus	6.2 — 50.0
S. albus	50.0
Streptococcus pyogenes	12.5
Vibrio cholerae Inaba 569B	25.0
V. cholerae El Tor Ogawa	50.0
Xanthomonas citri	3.1
X. malvacearum	6.2
X. campestris	12.5
Erwinia carotovora	100
Pseudomonas mangiferae	>100
P. solanacearum	>100
Candida utilis	12.5
C. albicans	12.5
C. tropicalis	3.1
Sporotrichum schenkii	6.2

preparations made from berberine treated vibrios (*V. cholrae* and *V. cholerae* biotype El Tor) not included active choleragenic toxin[31] and that oral administration of berberine prevented toxin-induced diarrhea in experimental choleragenic animals.[32]

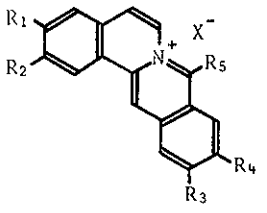
2 Antileukemic activity

Berberine has been shown to possess the cytotoxic[33] and neoplasm inhibitory effects [34] against KB and Ehrlich ascites tumor cells. Coralyne chloride[35] 72a, a hexadehydroberberinium salt, was recently found to exhibit antileukemic activity against both the P-388 and L-1210 strains in mice.[36,37] Analogs of coralyne containing the N-O-O trianglular pharmacophore[38] were synthesized for the study of the structure-activity relationship. Data of antileukemic activities of coralyne salts, its analogs and related compounds in Table V are cited from the paper of Zee-Cheng et al. Of greater interest was noted that two bis(methylenedioxy) analogs 73c and 73f showed activity against human epidermoid carcinoma of the nasopharynx (KB) *in vitro*. There is good reason to believe that these activities are associated with its ready formation of a stable complex with thymus DNA.[41]



72a X=Cl

b X=$C_2H_3SO_5$



73a $R_1+R_2=OCH_2O$, $R_3=R_4=OCH_3$, $R_5=CH_3$

b $R_1=R_2=OCH_3$, $R_3+R_4=OCH_2O$, $R_5=CH_3$

c $R_1+R_2=R_3+R_4=OCH_2O$, $R_5=CH_3$

d $R_1=R_2=R_3=R_4=OCH_3$, $R_5=C_2H_5$

e $R_1=R_2=R_3=R_4=OCH_3$, $R_5=n\text{-}C_3H_7$

f $R_1+R_2=R_3+R_4=OCH_2O$, $R_5=C_2H_5$

g $R_1=R_2=R_3=R_4=OCH_3$, $R_5=H$

h $R_1=R_2=H$, $R_3=R_4=OCH_3$, $R_5=CH_3$

i $R_1=R_2=R_3=OCH_3$, $R_4=H$, $R_5=CH_3$

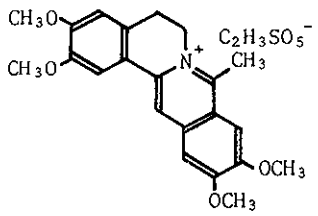


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Table V Antileukemic Activity of Coralyne and Analogs

Compound	P 388		L 1210	
	Dose (mg/Kg)	T/C*(%)	Dose (mg/Kg)	T/C*(%)
72a	400	167	400	139
	300	181	200	136
	200	181	100	134
	100	167		
	50	169		
	25	153		
72b	400	195	400	109
	300	193	256	130
	200	179	200	130
	160	163	100	126
	100	166	64	125
	75	169	50	124
	40	166		
	20	165		
	5	157		
73a (X = $C_2H_3SO_5$)			100	105
			50	122
			25	134
			11	107
73b (X = $C_2H_3SO_5$)			200	93
			100	121
			50	102
			25	144
			12	133
73c (X = $C_2H_3SO_5$)	25	95	100	70
	18.7	125	25	90
	12.5	173	12.5	129
	8.33	186	8.3	128
	6.25	170	6.2	116
	5.56	163		

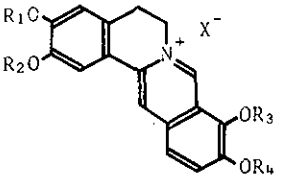
Table V (continued)

Compound	P 388 Dose (mg/Kg)	P 388 T/C* (%)	L 1210 Dose (mg/Kg)	L 1210 T/C* (%)
73d (X = $C_3H_5SO_5$)	200	181	400	121
	100	219	300	127
	50	215	200	136
			150	156
			100	142
			66	150
			44	147
73e (X = $C_4H_7SO_5$)			200	110
			100	100
73f (X = $C_3H_5SO_5$)			25	72
			12.5	114
			6.25	110
			3.13	118
73g (X = Cl)	320	77	320	93
	160	166	160	114
	80	154	80	111
	40	143	40	119
	20	145	20	117
	10	118	10	92
	5	109		
73h (X = $C_2H_3SO_5$)	80	59		
	40	102		
	20	111		
	10	152		
	5	147		
	2.5	140		
73i (X = $C_2H_3SO_5$)	200	109		
	100	145		
	50	167		
	33	186		
74			100	116
			50	107
			25	104

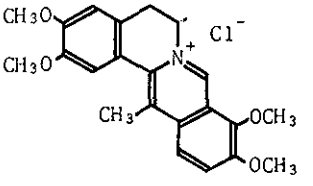
* The general screening procedure and the interpretation of data are carried out according to the references 39 and 40.

3 Uterine stimulating effect

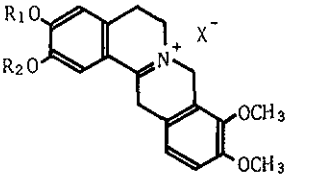
As the multiplicity of biological activities of the berberine alkaloids their uterine stimulating activity can be described. Certain berberine-containing plants have been used as folkloric antifertility remedies.[42] Among them, water-decoction of *Berberis aristata* (Berberidaceae) was known as folkloric abortifacient[43] in India and juice of *Chelidonium majus* (Papaveraceae) was drunk for folkloric antifertility use[44] in Soviet Union. *Argemone mexicana* (Papaveraceae) has been stated to be abortifacient or emmenagogue[45] in India.



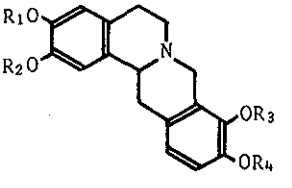
75 $R_1+R_2=CH_2$, $R_3=R_4=CH_3$
76 $R_1=R_2=R_3=R_4=CH_3$
77 $R_1=H$, $R_2=R_3=R_4=CH_3$
78 $R_1+R_2=R_3+R_4=CH_2$



79



80 $R_1+R_2=CH_2$
81 $R_1=R_2=CH_3$



82 $R_1+R_2=CH_2$, $R_3=R_4=CH_3$
83 $R_1=R_2=R_3=R_4=CH_3$
84 $R_1=H$, $R_2=R_3=R_4=CH_3$
85 $R_1+R_2=CH_2$, $R_3=H$, $R_4=CH_3$

Emmenagogue, abortifacient, and uterine stimulant plants including the berberine alkaloids are selected from the review by Farnsworth et al.[42] in Table VI.

Contractive activities of tertiary and quaternary berberine-type alkaloids on isolated uterus of mice were studied.[46,47] Quarternary bases 75-81 caused marked contraction of uterus, whereas these exhibited only a weak spasmolitic activity on isolated intestine of mice. On the contrary, tetrahydro-bases 82-84 showed strong papaverine-like action, however, their contractive activities on uterus were transitory. Data of minimum effective concentration are collected in Table VII.

Table VII Minimum Effective Concentration of Alkaloids on Maximum Contraction of Uteri

Berberine chloride 75	2×10^{-5} (g/ml)
Palmatine chloride 76	5×10^{-5}
Jatrorrhizine chloride 77	7.5×10^{-5}
Coptisine chloride 78	5.0×10^{-5}
Dehydrocorydaline chloride 79	7.5×10^{-5}
Dihydroberberine chloride 80	2×10^{-5}
Dihydropalmatine chloride 81	5×10^{-5}
Canadine 82	5.0×10^{-6}
Tetrahydropalmatine 83	7.5×10^{-6}
Tetrahydrojatrorrhizine 84	$2.5\text{-}5.0 \times 10^{-5}$

4 Antiulcerous and gastric antisecretory activities

The tuber of the genus *Corydalis* (Papaveraceae) have been used as an analgesic and a spasmolytic for the stomach-ache in Japanese and Chinese folk medicines. The pharmacological studies on the extracts and alkaloids obtained from the several *Corydalis* have been reported by several authors.[47-50] Recently, dehydrocorydaline chloride 79, a major quaternary alkaloid of *C. bulbosa*,[51] showed considerable gastric antisecretory activity.[52] Oral or s. c. administration prevented experimental gastric and duodenal ulcers in rats and guinea

Table VI Emmenagogue, Abortifacient, and Uterine Stimulant Plants Including Berberine Alkaloids

Plant name	Type of activity**	Isolated active constituent(s)
Berberidaceae		
Berberis amurensis	U	—
	I	Jatrorrhizine
B. aristata	A, E	—
	I	Berberine, Palmatine
B. lycium	I	Berberine
B. thunbergii	U	—
	I	Berberine, Columbamine, Jatrorrhizine, Palmatine
B. vulgaris	U	Total alkaloids
	I	Berberine, Columbamine, Jatrorrhizine, Palmatine
Nandina domestica	I	Berberine, Jatrorrhizine, Nandinine (85)
Menispermaceae		
Arcangelisia flava	A	—
	I	Berberine, Columbamine, Palmatine, Jatrorrhizine
Jateorhiza columba	I	Jatrorrhizine, Palmatine
Tinospora bakis	E	—
	I	Berberine, Palmatine
Papaveraceae		
Argemone mexicana	A, E	—
	U	Total alkaloids
	I	Berberine
Chelidonium majus	U	—
	I	Berberine
Corydalis ambigua	I	Palmatine, Tetrahydropalmatine
C. incisa	I	Tetrahydropalmatine
C. tuberosa	I	Canadine, Tetrahydropalmatine

Table VI (continued)

Plant name	Type of activity**	Isolated active constituent(s)
Hunnemannia fumariaefolia	I	Berberine
Sanguinaria canadensis	A	—
	U	Total alkaloids
	I	Berberine
Ranunculaceae		
Coptis japonica	U	Crude alkaloids
	I	Berberine, Columbamine, Jatrorrhizine, Palmatine
Hydrastis canadensis	U	—
	I	Berberine, Canadine
Jateorhiza palmata	U	Crude alkaloids
	I	Palmatine
Rutaceae		
Evodia hortensis f. hortensis	E	—
	I	Berberine

** A = abortifacient, ecbolic, oxytocic (folkloric).
E = emmenagogue, affecting the menstrual cycle (folkloric).
U = uterine stimulant as shown by *in vitro* or *in vivo* tests in animals.
I = active substance isolated and shown to stimulate uterine tissue either *in vitro* or *in vivo*.

pigs.[52,53] After intervenous administration in mice dehydrocorydaline was concentrated in the perpheral area of hepatic lobules.[54]

5 Enzyme inhibitory activity

Berberine markedly inhibited acetylcholine-esterase[55] both *in vivo* and *in vitro*, thereby casing temporary decrease of blood pressure. Berberine also inhibited the action of tyrosine decarboxylase[56] and tryptophanase,[57] where berberine is an antagonist of pyridoxal phosphate, the coenzyme.

Coralyne salts were found to be more potent inhibitors of catechol *O*-methyltransferase than pyrogallol.[37]

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