Notes

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Central Depressant Action of Tetrahydroberberine and Its Derivatives

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Tetrahydropalmatine is known to have potent sedative and hypnotic action and the depressant effect on the central nervous system of some compounds to realted berberine was tested. The levorotatory isomer of tetrahydroberberine had a stronger activity among the synthesized compounds.

Corydalis spp. is a well-known analgesic in traditional Chinese medicine where its extract is used as an analgesic and a hypnotic. Several investigations[2-4], have shown that tetrahydropalmatine contain in these plants possesses analgesic, hypnotic, and sedative actions. The actions of tetrahydroberberine on the central nervous system was reported in the other paper,[5] and the present paper discusses selected central depressant screening of some tetrahydroberberine derivatives.

Experimental

Pharmacological studies were conducted on albino mice (18—20 g). The animal were maintained on a commercial diet and water given freely. All animal experiments were carried out at the ambient temperature of 23°±1°. Ten animals each were used in the drug-treated and control groups. The control animals reecived only the vehicle and the test compounds were suspended in 5% acacia solution. Compound No. **1**.[6] **2**—**4**,[7] **5**,[6,8] **6**—**8**,[7,8] **9**,**10**,[9] **11**,[6] **12**,[11] **14**—**17**, **18**, and **19**[12] were synthesized according to the methods described in their respective literature. Their spectral data and melting points were consistent with reported data. Satisfactory results were obtained in their elemental analyses. Compound (**13**) was newly synthesized by the Hofmann degradation of 6 and the optical resolution of (+)-tetrahydroberberine was made by the use of (+)- and (−)-di-*p*-toluoyltartaric acid (Fig. 1).

Hofmann Degradation of 8-Propyltetrahydroberberine, No. 6——A suspension of 0.8 g of 6 and 10 ml of MeI in 1 ml of MeOH was heated at 110° for 5 hr in a sealed tube, and the reaction mixture was concentrated. The crystalline product was collected and recrystallized from MeOH to 0.85 g of methiodide (yield, 78%), as colorless prisms, mp 224—225°. The methiodide was suspended in 3 ml of MeOH, 10 ml of MeOH 15% KOH solution was added, and refluxed for 5 hr. The solvent was evaporated and the residue was extracted with ether. Ether extract was washed with H_2O, dried over anhyd. $MgSO_4$, and evaporated to give 0.7 g of yellow oil. This product was submitted to column chromatography over silica gel, and the column was eluted with $CHCl_3$ to afford colorless prisms (yield 60% from 6), mp 108—109°. NMR ($CDCl_3$): 8.99 (3H, t., J=3 Hz, C_8-H), 8.52—8.05 (4H, m, $-CH_2CH_2CH_3$), 7.84 (3H, s, N-CH_3), 6.13 (each 3H, s, OCH_3), 6.06 (1H, d, of d, J=10 Hz and J=2 Hz, $H\diagdown C{=}C\langle^{H}_{H}$), 4.54 (1H, d. of d., J=18 Hz and J=2 Hz $H\diagdown C{=}C\langle^{H}_{H}$), 4.09 (2H, s., OCH_2O), 3.24 (2H, s., arom. protons), 3.13 (1H, s., arom. proton), 2.97 (1H, s., arom. proton) 2.75 (1H, d.

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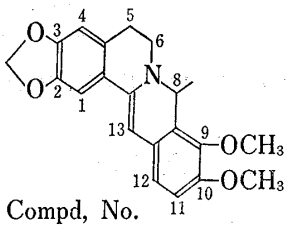
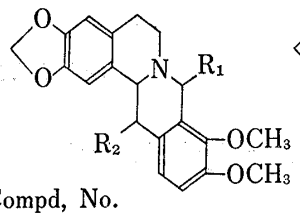
2) B. Hsu and K.C. Kin, *Arch. Int. Pharmacodyn.*, **129**, 318 (1962).
3) K.C. Kin, Y. Wang, and B. Hsu, *Acta Pharma. Sinica*, **11**, 754 (1964).
4) M.C. Chen and C.Y. Chi, *Acta Pharma. Sinica*, **12**, 185 (1965).
5) J. Yamahara, submitted to *Folia Pharmacol. Jpn.*
6) J.R. Grear and I.D. Spenser *Can. J. Chem.*, **41**, 783 (1963).
7) C. Tani and K. Ishibashi, *Yakugaku Zasshi*, **74**, 317 (1954).
8) von M. Freund and H. Commessmann, *Ann. Chem.*, **397**, 57 (1913).
9) T. Takemoto and T. Kondo, *Yakugaku Zasshi*, **82**, 1408 (1962).
10) I. Sallay and R.H. Ayers, *Tetrahedron*, **19**, 1397 (1963).
11) F.I. Pyman, *J. Chem. Soc.*, **103**, 817 (1913).
12) C. Tani, S. Takao, and M. Sugiura, *Yakugaku Zasshi*, **90**, 1012 (1970).



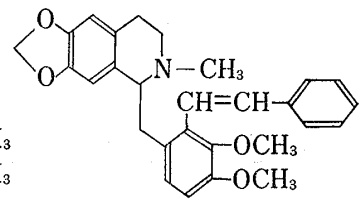
Compd, No.

1 : R=$CH_2C_6H_5$
2 : R=n-C_3H_7
3 : R=$CH(CH_3)_2$
4 : R=n-C_4H_9



Compd, No.

5 : R_1=$CH_2C_6H_5$, R_2=H
6 : R_1=n-C_3H_7, R_2=H
7 : R_1=$CH(CH_3)_2$, R_2=H
8 : R_1=n-C_4H_9, R_2=H
9 : R_1=H R_2=CH_3
10 : R_1=H R_2=C_2H_5



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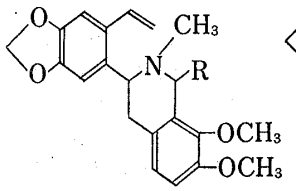
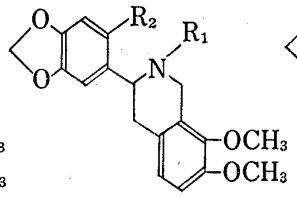
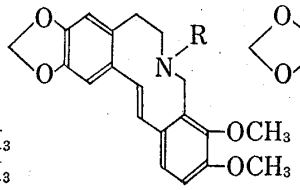


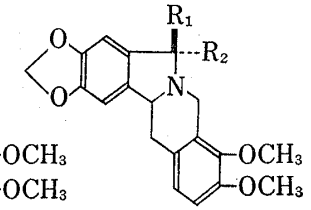
12 : R=H
13 : R=n-C_3H_7



14 : R_1=C≡N, R_2=CH_2CH_2Br
16 : R_1=$CONH_2$, R_2=$CH=CH_2$



15 : R=C≡N
17 : R=$CONH_2$



18 : R_1=H, R_2=CH_3
19 : R_1=CH_3, R_2=H

Fig. 1. Compounds Related to Berberine

J=18 Hz and J=10 Hz, $-CH=CH_2$). *Anal.* Calcd. for $C_{24}H_{29}O_4N$: C, 72.88; H, 7.39. Found: C, 72.76; H, 7.24.

Optical Resolution of (±)-Tetrahydroberberine into (+)-Tetrahydroberberine and (−)-Tetrahydroberberine——(−)-Di-*p*-toluoyltartaric acid (1.1 g) was added to the solution of (±)-tetrahydroberberine (1 g) in the minimum amount of MeOH, and allowed to stand for 1 week at room temperature. Precipitated yellow crystals were collected and recrystallized from MeOH to 0.3 g of (+)-tetrahydroberberine (−)-di-*p*-toluoyltartrate as yellow needles, mp 178° (yield 60%), $[\alpha]_D^{30}$ +85.5 (c=1.0 in $CHCl_3$). The di-*p*-toluoyltartrate was dissolved 3 volumes of $CHCl_3$, and extracted with 10% Na_2CO_3 solution. The $CHCl_3$ layer was washed with H_2O, dried over K_2CO_3, and evaporated. The residue was recrystallized from Me_2CO_3–MeOH to give (+)-tetrahydroberberine, mp 132°, $[\alpha]_D^{25}$ +302.5 (c=0.97 in $CHCl_3$). (+)-Di-*p*-toluoyltartaric acid (3.3 g) was added to a solution of (±)-tetrahydroberberine (3 g) in the minimum amount of MeOH, and processed in the same manner as above to give 1.2 g of (−)-tetrahydroberberine-(+)-di-*p*-toluoyltartrate as yellow needles, mp 174—175° (yield, 80%), $[\alpha]_D^{30}$ −87.2, and then (−)-tetrahydroberberine, mp 131—132°, $[\alpha]_D^{25}$ −298° (c=1.05 in $CHCl_3$). Infrared (IR) and NMR spectra of (+)-tetrahydroberberine and (−)-tetrahydroberberine were superimposable over those of the authentic tetrahydroberberine sample.

Spontaneous Motility: Motility of mice was measured using a Nihon Ikakikai Spontaneous Motor Activity Counter with 10 animals for 60 min, starting always 60 min after administration of the test compounds as described in the previous paper.[5]

Hexobarbital–Na Sleeping Time: Test compounds, 10—20 mg/kg, given orally or an equivalent volume of the vehicle, were administered 60 min before intraperitoneal of 70 mg/kg of hexobarbital–Na. Sleeping time was taken the time between the loss and return of the righting reflex.

Effect on Normal Body Temperature: The rectal temperature of rats was measured at 30 min intervals for 180 min after the administration of the tested compound, using an Omron MC-320 thermister thermometer. Tetrahydroberberine derivatives in a dose of 50 and 100 mg/kg given orally, or an equivalent volume of the vehicle, were injected into groups of 10 rats each.

Effect of Pentylentetrazol and Inclined Screening: Sixty minutes after the oral administration of the test compound (100—200 mg/kg), all the animals were tested for anticonvulsant activity by the Pentylentetrazol-induced convulsion technique. Muscle-relaxant activity was tested by the inclined screen method.[13]

Results

Effect on Spontaneous Motility

Table I illustrates the effect of tetrahydroberberine and its derivatives on spontaneous motility. (−)-Tetrahydroberberine was 2 times more active than (±)-tetrahydroberberine.

13) L.O. Randall and B. Kappel, "Benzodiazepines" ed. by S. Garaffnie, E. Mussini, L.O. Randall, Raven press, New York, 1973, p. 27.

Table I. Effect of THB Related Compounds on Spontaneous Motor Activity in Mice (Average of 10 mice)

Compound	Dose (mg/kg) *p.o.*	Percent of control (min)					
		10	20	30	40	50	60
Control	—	100.0	101.1	95.0	92.8	78.0	70.9
Chlordiazepoxide	10	110.0	78.5	45.3	37.0	18.0	10.0
Chlorpromazine-HCl	10	96.0	70.4	39.5	29.9	15.0	11.0
Berberine-HCl	50	98.5	90.4	89.3	89.0	79.0	67.0
(±)-THB	50	99.0	89.0	80.3	44.1	26.3	20.1
8-Propyl-DHB	50	101.0	94.0	80.3	70.4	84.3	80.0
8-Propyl-THB	50	95.3	90.1	80.2	51.1	28.3	22.2
8-Isopropyl-DHB	50	112.0	110.0	90.5	88.4	78.0	78.0
(±)-THB	50	102.1	94.3	77.3	43.1	20.5	19.2
8-Isopropyl-THB	50	95.6	89.0	80.3	40.1	27.0	20.5
8-Butyl-DHB	50	100.1	94.9	80.3	80.6	70.5	69.2
8-Butyl-THB	50	100.0	97.3	78.0	67.3	55.3	45.0
8-Benzyl-DHB	50	98.0	89.0	80.0	80.0	77.3	60.9
8-Benzyl-THB	50	104.0	94.7	67.0	50.3	33.3	30.1
Control	—	100.0	110.1	97.3	98.0	80.0	78.4
(±)-THB	50	100.5	98.4	90.3	50.1	23.3	20.2
13-Methyl-DHB	50	105.4	89.0	78.0	77.9	80.9	78.4
13-Methyl-THB	50	97.0	82.8	79.6	56.0	35.5	30.1
13-Ethyl-DHB	50	91.1	90.8	78.0	88.0	70.5	70.1
13-Ethyl-THB	50	90.1	88.3	70.1	44.0	30.5	27.0
No. **11**	50	100.4	104.5	85.0	87.0	78.5	69.0
No. **12**	50	97.7	90.5	91.3	79.0	77.3	70.1
No. **13**	50	104.0	94.3	81.0	79.0	70.3	70.1
No. **14**	50	95.9	93.1	79.0	70.1	70.9	69.3
No. **15**	50	105.7	89.4	88.1	70.4	70.5	70.2
No. **16**	50	93.1	83.1	90.4	77.8	70.5	64.0
No. **17**	50	94.9	90.1	89.3	70.4	72.8	67.1
No. **18**	50	93.1	90.5	79.1	87.7	69.0	60.3
No. **19**	50	100.5	90.3	78.1	78.9	60.1	65.4
(−)-THB	50	95.0	94.0	80.2	33.7	16.1	14.0
(+)-THB	50	100.4	93.3	80.1	80.3	78.0	70.5
(±)-THB	50	93.0	90.5	74.0	45.0	23.5	20.7

Prolongation of Sleeping Time Induced by Hexobarbital-Na

The most active of tetrahydroberberine derivatives in this test was (−)-THB which showed about 1.5 times stronger sedative effect than (±)-tetrahydroberberine. Test compounds substituted at C-8 and C-13 (No. **1**—**10**) were weakly active. The prolongation effect diminished almost to zero on dihydroberberine analogs and other compounds (No. **11**—**19**) (Table II).

Hypothermia, Antipentylentetrazol, and Inclined Screening

No significant results were observed in these test.

Discussion

The sedative-tranquilling actions of tetrahydropalmatine, an analog of tetrahydroberberine, are known.[2,4] The potency of central depressant action of tetrahydroberberine was similar to that of tetrahydropalmatine. Tetrahydroberberine and tetrahydropalmatine would be employed similary. A detailed description of (−)-tetrahydroberberine which showed 1.5—2.0 times stronger sedative effect than (±)-tetrahydroberberine was given in our previous paper.[5] The present report deals with comparisons of tetrahydroberberine and its derivatives

Table II. Effect of THB-related Compound on Hexobarbital-Na Hypnosis in Mice (Average of 10 mice)

With combined use of	Dose (mg/kg) *p.o.*	Sleeping time (min) mean±SE	Compound	Dose (mg/kg) *p.o.*	Sleeping time (min) mean±SE
Control	—	37.5± 3.5	Control	—	38.5±3.0
Nitrazepam	20	103.7±10.4	13-Methyl-DHB	20	36.7±3.3
Chlordiazepoxide	10	93.5± 8.8	13-Methyl-THB	20	50.1±3.3
Chlorpromazine-HCl	10	110.7± 6.0	13-Ethyl-DHB	20	35.7±2.9
Berberine-HCl	250	40.1± 2.0	13-Ethyl-THB	20	50.1±2.9
8-Propyl-DHB	10	40.5± 3.9	Control	—	36.8±4.0
	20	45.0± 5.2	No. 11	20	34.5±2.9
8-Propyl-THB	20	60.5± 4.3	No. 12	20	35.5±3.9
	40	78.5± 4.3	No. 13	20	40.0±2.7
(±)-THB	20	58.9± 4.8	No. 14	20	34.7±3.3
8-Isopropyl-DHB	20	43.2± 7.3	No. 15	20	30.5±5.5
8-Isopropyl-THB	20	58.5± 4.5	No. 16	20	33.5±2.9
8-Butyl-DHB	20	39.0± 4.9	No. 17	20	37.8±3.0
8-Butyl-THB	20	69.3± 6.0	No. 18	20	33.2±4.6
8-Benzyl-DHB	20	38.9± 2.0	No. 19	20	30.5±4.5
(±)-THB	20	60.0± 5.7	Control	—	36.5±2.7
8-Benzyl-THB	20	66.1± 4.3	(−)-THB	20	85.3±3.2
(−)-THB	20	89.0± 3.3	(+)-THB	20	45.1±4.4
	40	97.5± 7.0			
(+)-THB	20	45.7± 3.3			

with benzodiazepines and other central depressants. It became apparent that dihydroberberine derivatives and the compound No. **11—19**, were completely inactive, and tetrahydro derivatives substituted at C-8 and C-13 were nearly equipotent to (±)-tetrahydroberberine. From the study of structure-activity relationships, it was found that, for maintaining the central depressant action of tetrahydroberberine presence of a berberine-type skeleton is of great importance. (−)-Tetrahydroberberine was the most active of the tested berberine-related compounds, but it was less active than benzodiazepines.