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Inhibition of Adenosine 3′,5′-Cyclic Monophosphate Phosphodiesterase by Alkaloids. II[1)]

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The structure–inhibitory activity relationships were studied in analogous alkaloids from *Picrasma quassioides* and *Ailanthus altissima*, and their derivatives. Altogether, 53 β-carboline, 18 canthinone and 7 dimeric alkaloids were tested for cyclic adenosine monophosphate (cAMP) phosphodiesterase inhibition. Major alkaloids (**10**, **63** and **74**) among the three groups of congeners in *Picrasma quassioides* and *Ailanthus altissima* showed the most potent inhibitory activity, equal to or greater than that of papaverine used as a reference.

Keywords——cAMP phosphodiesterase; inhibitor; *Picrasma quassioides*; *Ailanthus altissima*; alkaloid; β-carboline; canthinone

Cyclic adenosine monophosphate (cAMP) phosphodiesterase inhibitors present in *Picrasma quassioides* BENNET and *Ailanthus altissima* SWINGLE have been identified as alkaloids.[2)] This paper deals with the structure–inhibitory activity relationships in the alkaloids present in *Picrasma quassioides* and *Ailanthus altissima*, and their derivatives.

Results and Discussion

The alkaloids isolated from *Picrasma quassioides* and *Ailanthus altissima* can be divided into three groups of congenars, β-carboline, canthinone and dimeric alkaloids. In total, 53 β-carboline alkaloids including 24 natural products, 18 canthinone alkaloids including 15 natural products and 7 dimeric alkaloids including 6 natural products were tested for inhibitory activity against cAMP phosphodiesterase in order to elucidate the structure–activity relationships. The results are summarized in Table I. The results[2)] reported previously are included for comparison and for discussion of the structure–activity relationships.

Among the β-carboline congeners (**1**—**53**), β-carboline with a methoxycarbonyl group at C-1 or -3 (**10**, **24**, **32**, and **42**) showed potent inhibitory effects. In the case of mono-substituted β-carboline (**2**—**20** and **25**), the following results were obtained. β-Carbolines with a methyl, an ethyl or a propyl group at C-1 have no inhibitory activity, but that with an isopropyl group has strong inhibitory activity. The introduction (**6**) of an alcohol group into β-carboline (**1**) at C-1 did not increase the inhibitory activity, but the introduction (**8**, **9** and **12**) of an aldehyde or carboxylic acid group into **1** did cause an increase, and methyl esters (**10** and **13**) were more effective than the corresponding acids (**9** and **12**, respectively). The introduction (**20**, **21** and **24**) of N-oxide into **1**, **2** and **10** increased the inhibitory activity by several ten-fold.

In the di- or tri-substituted β-carbolines (**21**—**24**, **26**—**28** and **29**—**53**) the results were as follows. O-Methylated β-carbolines (**35**, **40**, **44**, **47** and **51**) and O-acetylated β-carbolines (**45** and **48**) have higher inhibitory activity than the corresponding hydroxy β-carbolines (**34**, **39**,

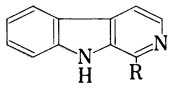
TABLE I. Inhibitory Activity on cAMP Phosphodiesterase and Sources of Alkaloids Assayed for the Inhibitory Activity

Compd. No.	IC_{50} ($\times 10^{-5}$ M)	Source	Reference	Compd. No.	IC_{50} ($\times 10^{-5}$ M)	Source	Reference
Papaverine	3.0	C.r.					
1	87.5	C.r.	2	**40**	4.6	A.a.	2
2	57.5	C.r.	2	**41**	44.6	A.a.	2
3	52.8	P.j.	3	**42**	10.5	D.n.	2
4	59.8	S.p.		**43**	25.2	P.q.	6
5	1.9	S.p.		**44**	4.9	P.q.	2
6	>200	P.q.	2	**45**	20.4	P.q.	6
7	6.5	S.p.		**46**	26.5	P.q.	6
8	24.9	P.q.	2	**47**	8.0	P.q.	6
9	9.6	S.p.	2	**48**	0.4	P.q.	6
10	3.6	P.q.	2	**49**	22.7	P.q.	2
11	18.1	P.q.	2	**50**	29.2	P.q.	6
12	16.5	A.a.	2	**51**	15.8	P.q.	6
13	0.6	D.n.		**52**	70.5	P.q.	7
14	0.2	S.p.		**53**	4.9	P.q.	2
15	24.0	S.p.		**54**	164	A.a.	2
16	53.8	P.q.	2	**55**	3.0	A.a.	
17	92.0	A.a.	2	**56**	>200	A.a.	2
18	33.7	S.p.	2	**57**	22.3	S.a.	2
19	44.8	S.p.	2	**58**	70.8	P.q.	2
20	2.8	S.p.		**59**	4.8	A.a.	2
21	1.1	S.p.		**60**	>200	A.a.	2
22	67.9	D.n.		**61**	>200	A.a.	2
23	>200	S.p.		**62**	9.1	P.q.	8
24	0.2	D.n.		**63**	1.4	P.q.	2
25	89.0	S.p.		**64**	10.4	P.q.	2
26	>200	S.p.	2	**65**	12.4	S.c.	2
27	30.7	S.p.	2	**66**	48.0	D.n.	7
28	>200	C.r.		**67**	29.7	S.c.	2
29	17.7	S.p.		**68**	>200	P.q.	9
30	22.1	S.p.	2	**69**	8.9	S.p.	
31	113	S.p.	2	**70**	24.0	S.p.	
32	1.7	S.p.	2	**71**	195	P.q.	9
33	22.9	S.p.	2	**72**	>200	P.q.	2
34	96.9	C.r.	2	**73**	5.1	P.q.	2
35	69.3	C.r.	2	**74**	3.0	P.q.	10
36	10.6	P.q.	2	**75**	4.9	P.q.	11
37	21.6	P.q.	2	**76**	0.5	D.n.	11
38	10.5	A.a.	2	**77**	0.2	P.q.	8
39	43.4	A.a.	2	**78**	9.6	P.q.	9

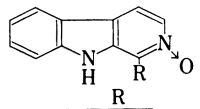
IC_{50} is the concentration of a compound required for 50% inhibition of cAMP phosphodiesterase activity. C.r., commercial reagent; P.j., *Picrasma javanica*; S.p., synthetic product; P.q., *Picrasma quassioides*; A.a., *Ailanthus altissima*; S.a., *Simarouba amara*; S.c., *Simaba cuspidata*; D.n., derivative of natural product.

43, **46** and **50**). The dihydro and tetrahydro derivatives (**25**—**28**) used as synthetic intermediates were not potent inhibitors.

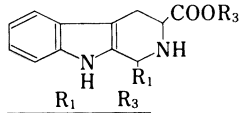
Among canthinone congeners (**54**—**71**), O-methylated canthinones (**56**, **58** and **64**) and O-acetylated canthinone (**66**) have lower inhibitory activity than the corresponding hydroxy canthinones (**55**, **57**, **62** and **63**). N-Substituted canthinones (**60**, **61** and **67**—**71**) were found to be almost ineffective except for **69**. These relationships in canthinone congeners, however, do not agree with the relationships in β-carboline congeners.



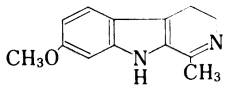
	R		R		R
1	H	8	CHO	14	OH
2	CH_3	9	COOH	15	OCH_3
3	CH_2CH_3	10	$COOCH_3$	16	$COCH_3$
4	$CH_2CH_2CH_3$	11	$COOCH_2CH_3$	17	$CONH_2$
5	$CH(CH_3)_2$	12	CH_2CH_2COOH	18	CH=CH-(C6H3(OCH3)2)
6	CH_2OH	13	$CH_2CH_2COOCH_3$	19	CH=CH-(C6H3(OCH3)2)
7	CH_2OCH_3				



	R
20	H
21	CH_3
22	CH_2CH_3
23	CH_2OCH_3
24	$COOCH_3$



	R_1	R_3
25	H	H
26	CH_3	H
27	CH_3	CH_3



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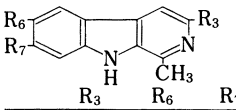
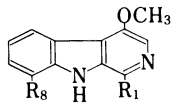


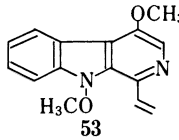
	R_3	R_6	R_7
29	$OCOCH_3$	H	H
30	CH_2OH	H	H
31	COOH	H	H
32	$COOCH_3$	H	H
33	H	NO_2	H
34	H	H	OH
35	H	H	OCH_3



	R_1	R_8
36	CH_2CH_3	H
37	$CH=CH_2$	H
38	CH_2CH_2OH	H
39	$CH(OH)CH_2OH$	H
40	$CH(OCH_3)CH_2OH$	H
41	$COCH_3$	H
42	$COOCH_3$	H

	R_1	R_8
43	CH_2CH_3	OH
44	CH_2CH_3	OCH_3
45	CH_2CH_3	$OCOCH_3$
46	$CH=CH_2$	OH
47	$CH=CH_2$	OCH_3
48	$CH=CH_2$	$OCOCH_3$
49	$CH_2CH_2OCH_3$	OCH_3

	R_1	R_8
50	$CH_2CH_2N(CH_2CH_3)_2$	OH
51	$CH_2CH_2N(CH_2CH_3)_2$	OCH_3
52	$COCH=CHCOOCH_3$	OCH_3



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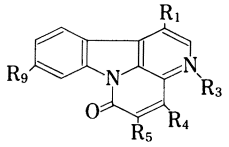
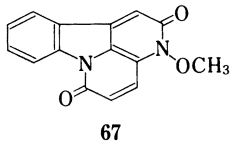


	R_1	R_5
54	H	H
55	OH	H
56	OCH_3	H
57	H	OH
58	H	OCH_3
59	H	CH_2OH

	R_1	R_3	R_4	R_5	R_9
60	H	O	H	H	H
61	OCH_3	O	H	H	H
62	H		OH	OCH_3	H
63	H		OCH_3	OH	H
64	H		OCH_3	OCH_3	H
65	H		H	H	OCH_3
66	H		OCH_3	$OCOCH_3$	H



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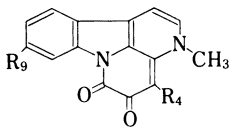
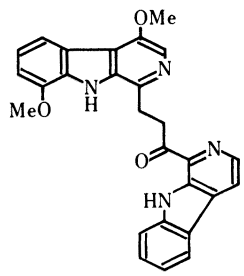


	R_4	R_9
68	H	H
69	H	OCH_3
70	CH_3	H
71	OCH_3	H

Most of the dimeric alkaloids showed comparatively high inhibitory activity except **72**. Major alkaloids (**10**, **63** and **74**) of the three groups of congeners in *Picrasma quassioides* and *Ailanthus altissima* showed the most potent inhibitory activity. Moreover, their inhibitory activity is equal to or greater than that of papaverine used as a reference.

Experimental

The following instruments were used for obtaining physical data. All melting points were determined with a micro-melting point apparatus and are uncorrected. The liquid scintillation counter used was an Aloka LSC-903. Silica gel 60 (Merck, precoated plate, 0.25 mm) was used for thin-layer chromatography (TLC) and detection was achieved by illumination with an ultraviolet (UV) lamp or by spraying Dragendorff's reagent. For column chromatography, silica gel (Fuji Davison Co., Ltd.) was used. The infrared (IR) spectra were recorded with a Hitachi 260-30 spectrometer. The mass spectra (MS) were measured with a JEOL JMS-D-300 mass spectrometer.



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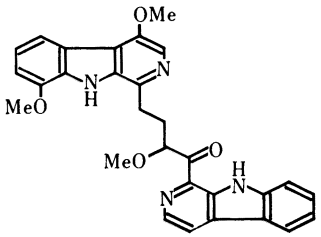

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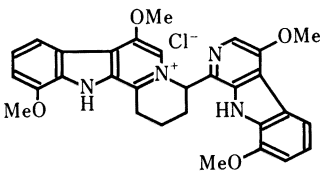

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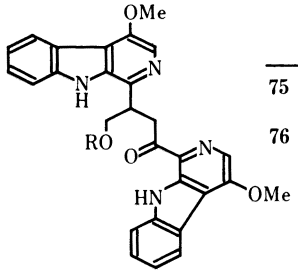
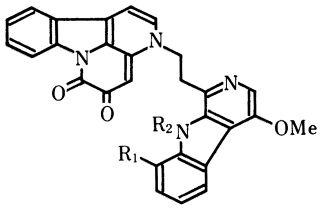


	R
75	H
76	Ac



	R_1	R_2
77	H	OMe
78	OMe	H

Assay Method for Inhibition of cAMP Phosphodiesterase——Samples were tested for cAMP phosphodiesterase inhibitory activity in duplicate by the method described in the previous paper.[2] All the inhibitors were added as solution in dimethylsulfoxide (DMSO). The presence of DMSO in the assay medium up to 2% concentration is known to have no effect on the enzyme activity. The IC_{50} value is the concentration of a compound required for 50% inhibition of cAMP phosphodiesterase activity.

Enzymes and Chemicals——Beef heart phosphodiesterase was purchased from Boehringer. Snake venom nucleotidase, cAMP, **1**, **2**, **34** and **35** were obtained from Sigma, and [^{3}H]cyclic AMP from the Radiochemical Centre. Papaverine (a reference inhibitor), DL-tryptophan, *n*-butylaldehyde, 1,1,2-trimethoxyethane and *p*-bromoperbenzoic acid were purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo); **28** was purchased from Nakarai.

Synthesis of Analogous Alkaloids——1-*n*-Propyl-*β*-carboline (**4**): **4** was prepared from DL-tryptophan and *n*-butylaldehyde by Snyder *et al.*'s method,[4] mp 218—219 °C. MS *m/z*: 210 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3430, 1620, 1560, 1320, 1240.

1-Isopropyl-*β*-carboline (**5**): **5** was prepared from DL-tryptophan and isobutylaldehyde by Snyder *et al.*'s method,[4] mp 170—171 °C. MS *m/z*: 210 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3440, 1620, 1560, 1330, 1240.

1-Methoxymethyl-*β*-carboline (**7**): **7** was prepared from DL-tryptophan and 1,1,2,-trimethoxyethane by Bradsher and Umans method,[5] mp 123—125 °C. MS *m/z*: 212 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3310, 1610, 1225, 1150, 1070.

13: **13** was prepared by treatment of *β*-carboline-1-propionic acid (**12**) with diazomethane, mp 115—117 °C. MS *m/z*: 254 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3350, 2970, 1720, 1240, 1180.

14: **14** was prepared by treatment of *β*-carboline 2-oxide (**20**) with acetic acid anhydride, mp 245—247 °C. MS *m/z*: 184 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3180, 2990, 1670, 1590, 1450, 1330, 1220, 950, 790, 740.

15: **15** was prepared by treatment of **14** with diazomethane, mp 258—259 °C. MS *m/z*: 198 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3120, 1660, 1590, 1560, 1330, 1270, 740.

20—24: **20—24** were prepared by treatment of **1—3**,**7** and **10**, respectively, with *p*-bromoperbenzoic acid. **20**, mp 268—271 °C. MS *m/z*: 184 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3440, 3125, 1610, 1250, 1150. **21**, mp 246—248 °C. MS *m/z*: 196 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3350, 3200, 1620, 1380, 1220, 1170. **22**, mp 212—216 °C. MS *m/z*: 212 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3050, 1620, 1320, 1200, 1180. **23**, mp 224—226 °C. MS *m/z*: 228 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3450, 1620, 1330, 1200, 1190. **24**, mp 224—226 °C. MS *m/z*: 228 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3450, 1620, 1330, 1200, 1190.

25: **25** was prepared from DL-tryptophan and formaldehyde by Snyder *et al.*'s method,[4] mp 285 °C (dec). MS *m/z*: 216 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3350, 3050, 1635, 1270, 1225, 1180, 1150, 1075.

29: **29** was prepared by treatment of **21** with acetic acid anhydride, mp 283 °C (dec.). MS *m/z*: 240 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3290, 2850, 1710, 1630, 1570, 1500, 1430, 1380, 1320, 1280, 1240, 1220, 1130, 1030, 820, 740.

55: mp > 300 °C. MS *m/z*: 236 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3450, 1660.

69: A mixture of harmine (**35**) and dimethyloxalate was heated for 20 min at 180 °C. The red reactant was recrystallized from MeOH to give **69**, mp > 300 °C. MS *m/z*: 280 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3450, 1695, 1650, 1590, 1550, 1520, 1470, 1270, 1220.

70: A mixture of **3** and dimethyloxalate was reacted for 20 min at 180 °C. The red reactant was recrystallized

from MeOH to give **70**, mp > 300 °C. MS *m/z*: 264 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3420, 1680, 1630, 1500, 1405.

References and Notes

1) A part of this study was presented at the 107th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April 1987. This paper forms Part XV of "Inhibitors of Cyclic AMP Phosphodiesterase in Medicinal Plants." Part XIV: T. Deyama, S. Nishibe, S. Kitagawa, Y. Ogihara, T. Takeda, T. Ohmoto, T. Nikaido and U. Sankawa, *Chem. Pharm. Bull.*, **36**, 435 (1988).
2) Y.-I. Sung, K. Koike, T. Nikaido, T. Ohmoto and U. Sankawa, *Chem. Pharm. Bull.*, **32**, 1872 (1984).
3) T. Ohmoto, K. Koike and K. Kagei, *Shoyakugaku Zasshi*, **41**, 338 (1987).
4) H. R. Snyder, C. H. Hansch, L. Katz, S. M. Parmerter and E. C. Spaeth, *J. Am. Chem. Soc.*, **70**, 219 (1948).
5) C. K. Bradsher and A. J. Umans, *J. Org. Chem.*, **28**, 3070 (1963).
6) T. Ohmoto, K. Koike, T. Higuchi and K. Ikeda, *Chem. Pharm. Bull.*, **33**, 3356 (1985).
7) T. Ohmoto and K. Koike, *Chem. Pharm. Bull.*, **32**, 3579 (1984).
8) T. Ohmoto and K. Koike, *Chem. Pharm. Bull.*, **33**, 4901 (1985).
9) T. Ohmoto and K. Koike, *Chem. Pharm. Bull.*, **33**, 3847 (1985).
10) K. Koike and T. Ohmoto, *Chem. Pharm. Bull.*, **35**, 3305 (1987).
11) K. Koike and T. Ohmoto, *Chem. Pharm. Bull.*, **34**, 2090 (1986).