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Inhibition of Adenosine 3',5'-Cyclic Monophosphate Phosphodiesterase by Alkaloids. II¹⁾

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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 congeners, 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 results²⁾ 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**,

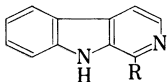
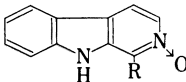
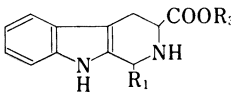
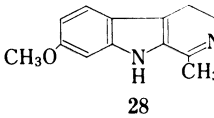
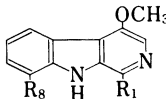
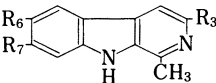
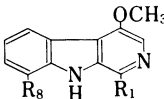
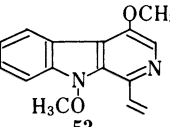
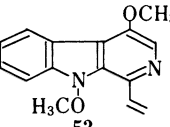
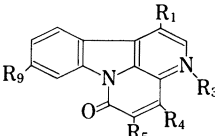
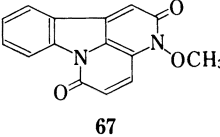
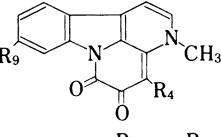
TABLE I. Inhibitory Activity on cAMP Phosphodiesterase and Sources of Alkaloids Assayed for the Inhibitory Activity

Compd. No.	IC ₅₀ (× 10 ⁻⁵ M)	Source	Reference	Compd. No.	IC ₅₀ (× 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

IC₅₀ 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.

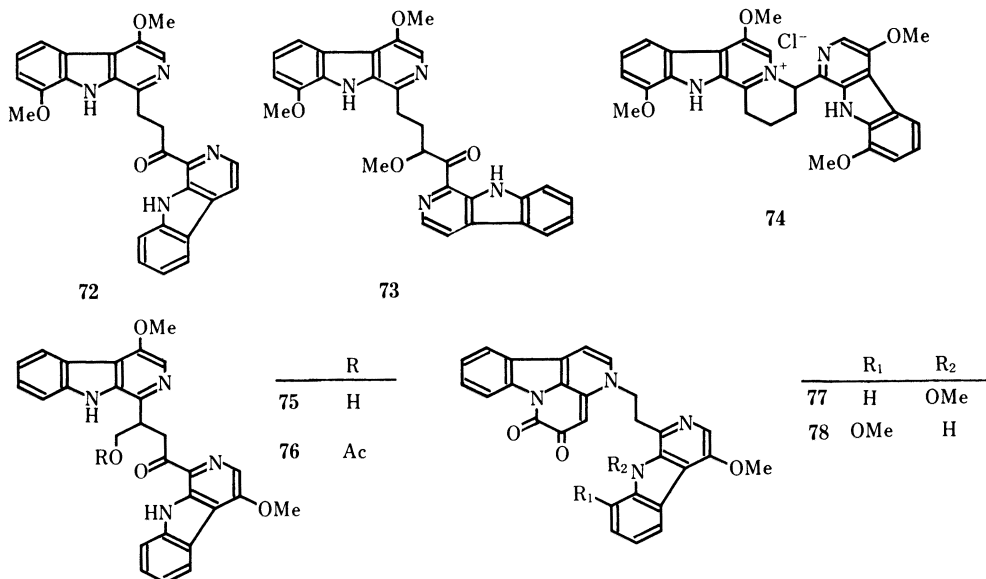
Among canthinone congeners (54—71), O-methylated canthinones (56, 58 and 64) and O-acetylated canthinone (66) have lower inhibitory activity than the corresponding hydroxy canthinones (55, 57, 62 and 63). N-Substituted canthinones (60, 61 and 67—71) were found to be almost ineffective except for 69. 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	20	H	25	H	H		
2	CH3	9	COOH	15	OCH3	21	CH3	26	CH3	H		
3	CH2CH3	10	COOCH3	16	COCH3	22	CH2CH3	27	CH3	CH3		
4	CH2CH2CH3	11	COOCH2CH3	17	CONH2	23	CH2OCH3					
5	CH<CH3	12	CH2CH2COOH	18	CH=CH- 	24	COOCH3					
6	CH2OH	13	CH2CH2COOCH3	19	CH=CH- 							
7	CH2OCH3											
												
R3 R6 R7			R1 R8			R1 R8			R1 R8			
29	OCOCH3	H	H	36	CH2CH3	H	43	CH2CH3	OH	50	CH2CH2N(CH2CH3)2	OH
30	CH2OH	H	H	37	CH=CH2	H	44	CH2CH3	OCH3	51	CH2CH2N(CH2CH3)2	OCH3
31	COOH	H	H	38	CH2CH2OH	H	45	CH2CH3	OCOCH3	52	COCH=CHCOOCH3	OCH3
32	COOCH3	H	H	39	CH(OH)CH2OH	H	46	CH=CH2	OH			
33	H	NO2	H	40	CH(OCH3)CH2OH	H	47	CH=CH2	OCH3			
34	H	H	OH	41	COCH3	H	48	CH=CH2	OCOCH3			
35	H	H	OCH3	42	COOCH3	H	49	CH2CH2OCH3	OCH3			
												
R1 R5			R1 R3 R4			R5 R9			R4 R9			
54	H	H	60	H	O	H	H	H	68	H	H	
55	OH	H	61	OCH3	O	H	H	H	69	H	OCH3	
56	OCH3	H	62	H	OH	OCH3	H	H	70	CH3	H	
57	H	OH	63	H	OCH3	OH	H	H	71	OCH3	H	
58	H	OCH3	64	H	OCH3	OCH3	H	H				
59	H	CH2OH	65	H	H	H	OCH3	H				
			66	H	OCH3	OCOCH3	H	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.



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 IC₅₀ 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 [³H]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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3440, 3125, 1610, 1250, 1150. **21**, mp 246–248 °C. MS *m/z*: 196 (M⁺). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3350, 3200, 1620, 1380, 1220, 1170. **22**, mp 212–216 °C. MS *m/z*: 212 (M⁺). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3050, 1620, 1320, 1200, 1180. **23**, mp 224–226 °C. MS *m/z*: 228 (M⁺). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3450, 1620, 1330, 1200, 1190. **24**, mp 224–226 °C. MS *m/z*: 228 (M⁺). IR $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 3420, 1680, 1630, 1500, 1405.

References and Notes

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