[Chem. Pharm. Bull. 25(8)1851—1855(1977)]

UDC 547.895.09 : 615.217.24.015.11.076.9

Studies on the α-Adrenolytic Activities of Apogalanthamine Analogs

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(Received October 12, 1976)

Apogalanthamine analogs were synthesized, and their α-adrenolytic and anti-5-HT activities and those of related compounds on rat aortic strips were compared with those of well known antagonists. It was found that N-alkylated 5,6,7,8-tetrahydrodibenz[*c*,*e*]-azocines (I—III) and N-alkylated 10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]-azocines (V—VII) had reversible α-adrenolytic activities; their activities were as great as those of phentolamine and benzylimidazoline. Of the compounds tested, DA-VIII-Me (II) had the strongest α-adrenolytic activity ($pA_2 = 8.76 \pm 0.07$); its activity was more than that of phentolamine.

Keywords——α-adrenolytic activity; rat aortic strips; apogalanthamine analogs; azocine derivatives; phentolamine; benzylimidazoline; galanthamine; anti-5-HT activity

Previously we reported[2] that a new compound with a 2-halogenoethylamine group, 6-(2-bromoethyl)-10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine[3] (DA–VIII–MBr), has an irreversible α-adrenolytic action and that it blocks the response of rat aortic strips to adrenaline more than their response to 5-hydroxytryptamine (5–HT). DA–VIII–MBr is an analog of apogalanthamine and we thought that other apogalanthamine analogs without a 2-halogenoethylamine group might have a reversible α-adrenolytic action. To test this possibility we synthesized derivatives of 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine as other analogs of apogalanthamine and tested their α-adrenolytic and anti-5-HT activities on rat aortic strips. We calculated the difference between these two activities to clarify the selectivities of their α-adrenolytic actions, because it is known that the response to 5–HT can be antagonized by α-adrenolytic agents, such as ergot alkaloids[4] and phentolamine.[5,6] Some of these analogs of apogalanthamine were found to be as strong α-adrenolytic agents as phentolamine and to be more specific against adrenaline than against 5–HT, but most of them inhibited the responses to both adrenaline and 5–HT. 6-Methyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine styphnate, abbreviated to DA–VIII–Me (II), was the most active and had a stronger effect than phentolamine.

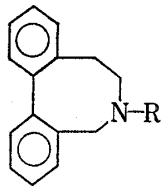
Methods and Materials

Pharmacological Activity——Strips of thoracic aorta were cut spirally from rats weighing 200 to 300 g, as described by Furchgott and Bhakrakom[7] and suspended in a 10 ml organ bath in modified Krebs-bicarbonate solution (composition in mM: NaCl, 118.2; KCl, 4.6; $CaCl_2$, 2.5; $MgSO_4$, 1.2; $NaHCO_3$, 24.8 and glucose, 10) at 36° bubbled with 5% CO_2 in oxygen. Contractions were recorded on the smoked drum of a kymograph with an isotonic lever weighing about 1.0 g.

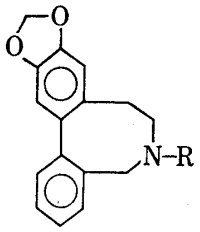
1) Location: *Shomachi 1-chome, Tokushima, 770, Japan.*
2) Y. Ishida, K. Watanabe, S. Kobayashi, and M. Kihara, *Jpn. J. Pharmacol.*, **26**, 607 (1976).
3) S. Kobayashi, M. Kihara, Y. Yamasaki, Y. Ishida, and K. Watanabe, *Chem. Pharm. Bull.* (Tokyo), **23**, 3036 (1975).
4) I.R. Innes, *Brit. J. Pharmacol. Chemother.*, **19**, 120, 429 (1962).
5) J.D. Kohli, *Brit. J. Pharmacol. Chemother.*, **32**, 273 (1968).
6) V.S.R. Krishnamurty, *Arch. Int. Pharmacodyn. Ther.*, **189**, 90 (1971).
7) R.F. Furchgott and S. Bhadrakom, *J. Pharmacol. Exp. Ther.*, **108**, 129 (1953).

A cumulative method[8] was used and inhibitory activity was estimated by recording the response curves for each agonist in the absence and presence of an antagonist. After equilibrating the strip for 2 hr with repeated washing, the cumulative response curve to an agonist was recorded 2 to 3 times at intervals of 30 min until the responses were the same in two successive recordings either in the absence or presence of antagonist. In each recording the exposured time of the strip to the antagonist was 15 min. Contractions were expressed as percentages of the maximal response to each agonist; the maximal responses to different agonists were not significantly different. The presence of a competitive antagonist resulted in a shift to higher concentration of the log dose-response curve to an agonist. The pA_2-value for competitive inhibition was calculated by the method of van Rossum[7] from the shift of the curve from the following equation: $pA_2 = pA_x + \log(x-1)$, where pA_x is a negative logarithm of the molar concentration of an antagonist causing a shift of x.

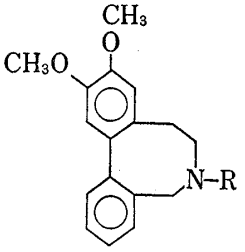
Materials——Apogalanthamine analogs were synthesized as described previously.[3,9-12] Their numbers, nomenclatures, abbreviations, and observed mp values were as follows: (I), 5,6,7,8-tetrahydro-



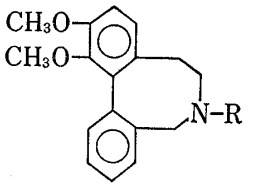
DA-VIII-R (I,II,III,IV)
I : R=H, II : R=CH_3,
III : R=C_2H_5, IV : R=CH_3CO



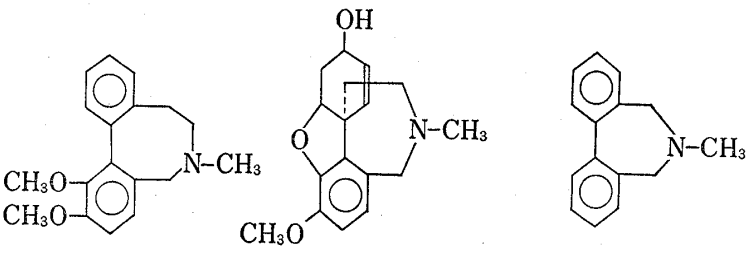
DA-VIII-M-R (V,VI,VII)
V : R=H, VI : R=CH_3, VII : R=C_2H_5



DA-VIII-MO-R (VIII,IX)
VIII : R=H, IX : R=CH_3



DA-VIII-isoMO-R (X,XI,XII)
X : R=H, XI : R=CH_3, XII : R=C_2H_5



XIII : O,O'-dimethyl-apogalanthamine
XIV : galanthamine
XV : DA-VII-Me

Chart 1. Structures of Apogalanthamine Analogs and Related Compounds
(Numbers in parentheses correspond to those Table I)

8) J.M. Van Rossum, *Arch. Int. Pharmacodyn. Ther.*, **143**, 299 (1963).
9) S. Kobayashi and S. Uyeo, *J. Chem. Soc.*, **638** (1957).
10) S. Kobayashi, T. Katayama, and M. Kihara, presented at the Chugoku-Shikoku Branch Meeting of the Pharmaceutical Society of Japan, May 18, (1974, Tokushima).
11) S. Kobayashi, M. Kihara, M. Shizu, and K. Kitahiro, presented at the 95th Annual Meeting of the Pharmaceutical Society of Japan, April 6 (1975, Nishinomiya).
12) S. Kobayashi, M. Kihara, S. Mieno, and M. Miura, presented at the 96th Annual Meeting of the Pharmaceutical Society of Japan, April 6 (1976, Nagoya).

dibenz[*c*,*e*]azocine,[12] (DA-VIII-H), mp 115—117°; (II), 6-methyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine styphnate,[12] (DA-VIII-Me), mp 193—194°; (III), 6-ethyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine styphnate,[12] (DA-VIII-Et), mp 174.5—175.5°; (IV), 6-acetyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine,[12] (DA-VIII-Ac), mp 105—106°; (V), 10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine,[3] (DA-VIII-M-H), mp 98.5—100°; (VI), 6-methyl-10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine styphnate,[13] (DA-VIII-M-Me), mp 216.5—217.5°; (VII), 6-ethyl-10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine,[3] (DA-VIII-M-Et), mp 78.5—81.5°; (VIII), 10,11-dimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine,[11] (DA-VIII-MO-H), mp 119—123°; (IX), 6-methyl-10,11-dimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine,[11] (DA-VIII-MO-Me), mp 72—73°; (X), 11,12-dimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine styphthnate,[10] (DA-VIII-isoMO-H), mp 186—188°; (XI), 6-methyl-11,12-dimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine picrate,[10] (DA-VIII-isoMO-Me), mp 175—177°; (XII), 6-ethyl-11,12-dimethoxy-5,6,7,8-tetrahydrodibenz-[*c*,*e*]azocine styphnate,[10] (DA-VIII-isoMO-Et), mp 192—193°; (XIII), O,O′-dimethylapogalanthamine styphnate,[9] mp 212.5—213°; (XIV), galanthamine hydrochloride,[14] mp 252—253°; and (XV), 6-methyl-5,6-dihydrodibenz[*c*,*e*]azepine hydrochloride,[15] (DA-VII-Me), mp 217—220°.

The other chemical reagents used were 1-epinephreine bitartrate, 5-hydroxytryptamine creatinine sulphate (5-HT), phentolamine mesylate, benzylimidazoline hydrochloride, yohimbine hydrochloride and 3-(2′-benzylaminoethyl)-5-methoxyindol hydrochloride (S-8).

1. Relative α-Adrenolytic and Anti-5-HT Activities of Apogalanthamine Analogs and Related Compounds: Almost all the apogalanthamine analogs exhibited both α-adrenolytic and anti-5-HT activity, shown in Table I. All the analogs in the DA-VIII-R and DA-VIII-M-R series, except DA-VIII-Ac (IV), were more active against adrenaline than against 5-HT. The order of the α-adrnolytic activities of the N-alkylated derivatives in the two series was Me>Et>H. Among the N-methyl derivatives the most active, DA-VIII-Me (II), was 5.8 times as active as phentolamine and the next, DA-VIII-M-Me (VI), was only slightly less potent than phentolamine. The anti-5-HT activities of the compounds in the two series were similar and showed no correlation with the nature of the N substituent.

Table I. α-Adrenolytic and Anti-5-HT Activities of Apogalanthamine Analogs and Related Compounds on Rat Aortic Strips

No.	R	pA_2		Ratio of activities[a]
		Against adrenaline	Against 5-HT	
DA-VIII-R				
I	H	7.23±0.10(10)[b]	6.25±0.09(6)	9.6:1
II	Me	8.76±0.07(8)	6.00±0.05(8)	575.0:1
III	Et	7.70±0.02(10)	5.88±0.10(6)	66.1:1
IV	Ac	5.46±0.08(6)	5.37±0.09(5)	1.2:1
DA-VIII-M-R				
V	H	7.17±0.08(7)	5.75±0.17(7)	26.3:1
VI	Me	7.71±0.05(8)	5.93±0.05(8)	60.3:1
VII	Et	7.40±0.06(9)	5.32±0.25(8)	74.2:1
DA-VIII-MO-R				
VIII	H	6.05±0.06(11)	5.87±0.06(10)	1.5:1
IX	Me	6.32±0.09(9)	5.67±0.13(6)	4.5:1
DA-VIII-isoMO-R				
X	H	5.44±0.20(4)	5.54±0.12(4)	0.8:1
XI	Me	5.05(2)	5.60(2)	0.3:1
XII	Et	5.02(2)	4.90(2)	1.3:1
XIII	O,O′-Dimethylapogalanthamine	6.97±0.05(9)	6.99±0.07(9)	1.0:1
Related compounds				
XIV	Galanthamine	6.16±0.15(5)	No effect[c]	
XV	DA-VII-Me	7.50±0.05(9)	5.48±0.07(7)	104.7:1

a) Anti-logarithm of the difference between the pA_2-values against adrenaline and 5-HT.
b) Mean±S.E., (number of experiments).
c) At concentrations of up to 10^{-5} g/ml.

13) This compound was prepared by treatment of V with formalin and sodium borohydride (The preparation will be reported elsewhere).
14) S. Uyeo and S. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **1**, 139 (1953).
15) J.O. Hawthorne, E.L. Mihelic, M.S. Morgan, and M.H. Milt, *J. Org. Chem.*, **28**, 2831 (1963).

The DA-VIII-MO- and DA-VIII-isoMO- analogs had weaker α-adrenolytic activities than the compounds of the other two series, and their α-adrenolytic and anti-5-HT activities were similar.

O,O′-Dimethylapogalanthamine (XIII) had the most activity against 5-HT of all the compounds tested, but its activities against 5-HT and against adrenaline were similar. Galanthamine (XIV), the parent alkaloid of apogalanthamine, had a weak α-adrenolytic activity, but had no activity against 5-HT at concentrations of up to 10^{-5} g/ml. DA-VII-Me (XV) with a 7-membered ring in the series of RO 2-3248 (Ilder)[16] was strongly α-adrenolytic.

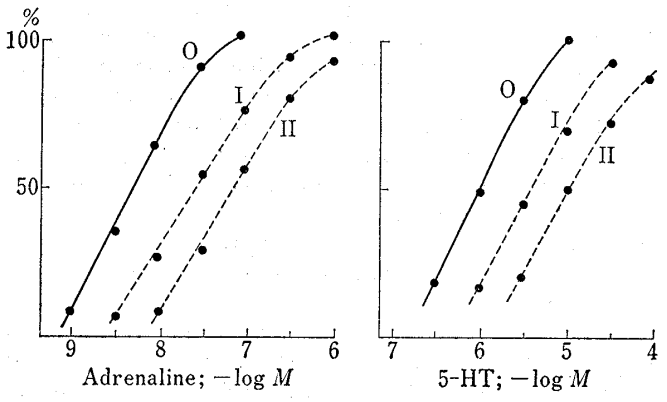


Fig. 1. log Dose-response Curves for Adrenaline and 5-HT in the Absence and Presence of DA-VIII-Me

(Left figure) 0, control curve for adrenaline; I and II, curves in the presence of DA-VIII-Me, 3×10^{-9} and 10^{-8} g/ml, respectively. (Right figure) 0, control curve for 5-HT; I and II, curves in the presence of DA-VIII-Me, 10^{-6} and 3×10^{-6} g/ml, respectively.

Most of the antagonists tested shifted the dose-response curves of adrenaline and 5-HT to the right without suppressing the maximal responses significantly. For example, the antagonistic effects of DA-VIII-Me on the two agonists are shown in Fig. 1. Its antagonistic effects on the two agonists seemed to be competitive and reversible. This work was confined to studies on the relative inhibitory effects of these analogs on adrenaline and 5-HT; the mechanisms of these effects were not investigated. However, the compounds with pA_2-values of above 6.0 seem to be truely competitive. The mechanisms of the effects of compounds with pA_2-values of under 6.0, especially against 5-HT, remain to be determined, because they might be expected to be non-specific.

2. Comparison of Representative Apogalanthamine Analogs with Well Known Antagonists: The effects of apogalanthamine analogs on aortic strips were compared with those of the α-adrenolytic agents, benzylimidazoline, yohimbine and phentolamine, and the anti-5-HT agent, 3-(2′-benzylaminoethyl)-5-methoxyindole (S-8).[17] The 6 compounds, I, II, III, V, VI, and VII shown in Table I had much stronger α-adrenolytic activities than benzylimidazoline, and the latter had no effect against 5-HT at concentration of up to 10^{-5} M. The α-adrenolytic activity of yohimbine was less than that of DA-VIII-Me (II), but similar to those of DA-VIII-Et (III) and DA-VIII-M-Me (VI); its activity against 5-HT was greater than those of II, III or VI.

Table II. Activities of Well Known Reversible Antagonists against Adrenaline and 5-HT

Compounds	pA_2		Ratio of activities[a]
	Against adrenaline	Against 5-HT	
Benzylimidazoline	6.91±0.13(6)[b]	No effect[c]	
Yohimbine	7.60±0.12(6)	6.38±0.10(6)	16.2:1
Phentolamine	8.00±0.18(6)	6.87±0.16(6)	12.3:1
S-8	6.22±0.34(6)	7.12±0.08(6)	0.1:1

a) Anti-logarithm of the difference between the pA_2-values against adrenaline and 5-HT.
b) Mean ±S.E., (number of experiments).
c) At concentrations of up to 10^{-5}M.

Krishnamurty[5] reported that the pA_2-values of phentolamine against noradrenaline and 5-HT in rat aorta were 7.94±0.05 and 7.09±0.10, respectively. We obtained similar values for adrenaline, instead of noradrenaline, and 5-HT. The inhibitor of 5-HT, S-8, inhibited the response to 5-HT more than that to adrenaline.

To compare the effects of the antagonists on the two agonists, we calculated the ratios of their pA_2-values against adrenaline and 5-HT, as the anti-logarithm of the difference between two pA_2-values. The α-adrenolytic activities of the DA-VIII- and DA-VIII-M- analogs were more specific than those of phentolamine and yohimbine, DA-VIII-Me being the strongest and the most specific.

16) L.O. Randall and T.H. Smith, *J. Pharmacol. Exp. Ther.*, **103**, 10 (1951).
17) K. Takagi, I. Takayanagi, T. Irikura, K. Nishino, M. Ito, and H. Ichinoseki, *Jpn. J. Pharmacol.*, **19**, 234 (1968).

Discussion

Previously we reported[2] that an DA–VIII-M-analog, DA–VIII–MBr, with a 2-halogenoethylamine attached to the nitrogen, has an irreversible α-adrenolytic action which is more selective than those of dibenamine and phenoxybenzamine. In this work we found that apogalanthamine analogs, especially the DA–VIII– and DA–VIII-M- analogs were a new type of reversible α-adrenolytic agent. From these results, DA–VIII– and DA–VIII-M- analogs must have some structural entity fitting the α-adrenoceptor either reversibly or irreversibly.

Apogalanthamine analogs have a similar structure to RO 2–3248 (Ilida)[16]: the former are dibenz[*c*,*e*]azocine derivatives with an 8-member ring, whereas Ro 2-3248 is dibenz[*c*,*e*]azepine derivative with a 7-membered ring. The N-methyl azocine derivatives, DA–VIII–Me (II) and DA–VIII-M-Me (VI), were more active than the azepine derivative, DA–VII–Me (XV), as Table I shows. Moore, *et al.*[18] reported that Ilida, an N-allyl azepine derivative, had a prolonged action, blocking the pressor response to adrenaline in dogs. Thus, the activity of N-allyl derivatives of apogalanthamine analogs must be studied.

Acknowledgement Thanks are due to Kyorin Chemical Laboratory for the gift of 3-(2′-benzylaminoethyl)-5-methoxyindol hydrochloride.

18) P.E. Moore, A.W. Richardson, and H.D. Green, *J. Pharmacol. Exp. Ther.*, **106**, 14 (1952).