NONCOINCIDENCE OF THE ANXIOLYTIC, SEDATIVE, AND ANTISPASMODIC PROPERTIES IN HARMAN DERIVATIVES

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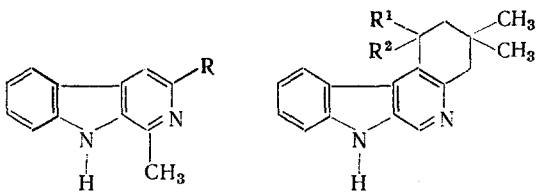
Many β-carbolines [8, 10], in particular, norharman [8], harman [8, 13], and esters of β-carboline-3-carboxylic acid [9, 10], interact with high affinity with the specific binding sites of benzodiazepine tranquilizers (BD) in membrane fragments of the brain. These ligands of the benzodiazepine receptors are considered as agonists (antibenzodiazepines), since they induce convulsions that can be eliminated with BD [14, 16], while certain β-carbolines have an anxiogenic effect [10, 11]. And yet, a number of harman derivatives are characterized by sedative and anesthesia-potentiating properties [2, 7], while harman in low doses exhibits anxiolytic activity [2].

This work presents the results of an investigation of the anxiolytic sedative, and antispasmodic properties of substituted β-carbolines (Ia-e and IIa-d).



Ia: R = H; Ib R = CH_3; Ic R = CO_2H; Id R = CO_2CH_3; Ie: R = $CONH_2$; IIa: R = CH_3; R^1 = H; R^2 = NH_2; IIb: R = CH_3; R^1R^2 = N—OH; IIc: R = CH_3; R^1R^2 = O; IId R = C_2H_5; R^1R^2 = O

Compounds Ia-d were synthesized according to the procedures described in [4, 15]. The amide Ie was produced by treating the chloride of harman carboxylic acid (Ic) with ammonia. The o-carboline IIa was synthesized according to a Leuckart reaction from 3,3,6-trimethyl-1-oxo-1,2,3,4-tetrahydroindolo[2,3-c]quinoline [5]. The interaction of the latter with hydroxylamine leads to the oxime IIb. To obtain compounds IIc and IId we used a method based on the ability of indolo[2,3-c]pyrylium salts to be converted to β-carboline derivatives under the action of ammonia. The initial pyrylium salts were produced by acylation of 2-(3'-indolyl)-dimedone [1] by trifluoroacetic acid anhydride and propionic acid anhydride in the presence of perchloric acid.

The data presented in this communication provide evidence that anxiolytic activity is characteristic of many harman derivatives and may be combined both with spasmodic and with antispasmodic activity, with the presence or with the absence of ability to potentiate the effects of barbiturates.

EXPERIMENTAL CHEMICAL PART

Amide of Harman-3-carboxylic Acid (Ie). A mixture of 2.3 g (0.01 mole) harman-3-carboxylic acid and 20 ml thionyl chloride was boiled with a reflux condenser for 3 h, the excess thionyl chloride was distilled off, 40 ml of benzene was added, and the solution was evaporated again. Then 50 ml of benzene was added to the residue, and the solution was saturated with gaseous ammonia. The precipitate formed was filtered off, washed with water, and dried.

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TABLE 1. Comparative Pharmacological Activity of Derivatives of β-Carboline Ia-e and IIa-d

Compound	Dose, mg/kg	In conflict situation		In behavioral tests on mice ($ED_{50} \pm S_{\bar{x} \cdot t}$), mg/kg				$LD_{50} \pm S_{\bar{x} \cdot t}$ (mice, intraperitoneally, mg/kg)
		Number of consumptions of water, $\bar{x} \pm S_{\bar{x} \cdot t}$ (control)	Number of approaches to the water dispenser; $\bar{x} \pm S_{\bar{x} \cdot t}$ (control)	Inhibition of motor activity	Enhancement of hexenal anesthesia	Activity		
						Anticorazole	Antipicrotoxin	
Ia	1	14,2±4,0* (5,2±0,6)	29,1±6,5 (18,6±4,1)	8,2±3,2	7,2±2,6	>40	>40	66±10
	5	3,8±1,0	18,2±8,5					
	10	5,4±1,6	11,7±4,4					
Ib	1	9,3±1,2*	17,4±5,1	22,0±8,0	56,0±10,0	>80	>80	123±10
	10	3,3±0,3*	11,0±2,7*					
Ic	1	6,2±0,8 (5,6±1,0)	27,3±7,1 (23,2±3,9)	18,5±4,4	50,8±7,6	>80	>80	>320
	10	4,3±0,5						
Id	1	14,0±5,6*	34,7±8,4*	15,3±5,2	28,6±8,0	>80	>80	180±28
	5	4,7±0,7	19,0±6,1					
	10	3,6±0,9*	7,6±2,7*					
Ie	1	5,9±1,3	25,5±4,3	29,8±6,6	66,6±16,0	>80	>80	170±12
IIa	1	8,5±3,3	15,0±11,1	8,0±2,8	>40	>40†	>40†	64±6,3
IIb	1	4,6±2,1	17,2±6,6	18,0±3,0	>80	>80†	>80†	240±30
IIc	1	6,1±1,2 (5,2±0,6)	26,5±5,1 (18,6±4,1)	4,8±1,6	13,4±4,2	>80	29,3±4,8	400±35
	10	10,1±2,1*	25,1±5,4					
IId	1	8,6±1,1*	19,6±6,3	8,0±1,6	32,3±6,2	51,6±5,2	5,5±1,4	186±52
	5	6,0±2,7	7,5±4,5					

*Differences from the control are significant ($P < 0.05$).
†Enhancement of the toxicity of convulsive poisons.

Yield of Ie 2 g (88%), mp 290-291°C (from aqueous ethanol). Found, %: C 74.57; H 5.30; N 20.01. $C_{19}H_{11}N_3O$. Calculated, %: C 74.62; H 5.30; N 20.10.

Dihydrochloride of 1-Amino-3,3,6-trimethyl-1,2,3,4-tetrahydroindolo-[2,3-c]quinoline (IIa). A 2.8 g (0.01 mole) portion of 1-oxo-3,3,6-trimethyl-1,2,3,5-tetrahydroindolo[2,3-c]-quinoline was dissolved in a mixture of 30 ml of formamide and 20 ml of 85% formic acid and heated with a reflux condenser for 60 h at a temperature of the reaction mixture 160-170°C. In the last 10 h, 5-7 ml of distillate was driven off, and the temperature was raised to 180°C. The cooled mixture was dissolved in 50 ml of ethanol, and aqueous ammonia was added to an alkaline pH. The precipitate of 1-formylamino-3,3,6-trimethyl-1,2,3,4-tetrahydroindolo-[2,3-c]-quinoline formed was filtered off and washed with water (mp 296-297°C from an ethanol-benzene mixture). To the precipitate we added 30 ml of ethanol, 15 ml concentrated hydrochloric acid, and 15 ml of water and boiled with a reflux condenser for 5 h, after which 40 ml of distillate was driven off, and the mixture was cooled. The precipitate formed was filtered off, obtaining 2.3 g (65%) of the dihydrochloride IIa with mp 319-320°C (from water). Found, %: C 61.65 H 7.10; Cl 20.26; N 12.46. $CL_8H_{21}N_3 \cdot 2HCl$. Calculated, %: C 61.36; H 6.58; Cl 20.13; N 11.93.

Hydrochloride of 1-Oximino-3,3,6-trimethyl-1,2,3,4-tetrahydroindolo-[2,3-c]quinoline (IIb). A mixture of 2.8 g (0.01 mole) 1-oxo-3,3,6-trimethyl-1,2,3,4,-tetrahydroindolo[2,3,-c]-quinoline and 0.93 g (0.13 mole) hydroxylamine hydrochloride in 50 ml of ethanol was boiled with a reflux condenser for 1 h, 25 ml of alcohol was distilled off, and the mixture was cooled. The precipitate formed was filtered and dried under vacuum. Yield of IIb 3 g (91%), mp 338-340°C (with dec.). Found, %: C 65.44; H 6.05; Cl 10.79; N 12.73. $C_{18}H_{20}N_3O \cdot HCl$. Calculated, %: C 65.55; H 6.11; Cl 10.75; N 12.74.

3,3-Dimethyl-6-trifluoromethyl-1-oxo-1,2,3,4-tetrahydroindolo[2,3-c]-benzopyrylium Perchlorate. To a mixture of 7 ml (0.05 mole) trifluoracetic anhydride and 3 ml trifluoro-acetic acid we added 2.55 g (0.01 mole) of 2-(3'-indolyl)-dimedone and left for 24 h at room temperature. To the bright red solution formed upon cooling to 5°C, we successively added 0.8 ml (0.01 mole) of 70% perchloric acid and 100 ml of absolute ether. The precipitate formed was filtered, washed with ether, and dried. Yield 2.9 g (67%), mp 220°C (with dec.; from acetic anhydride). Found, %: N 3.30. $C_{18}H_{15}ClF_3NO_6$. Calculated, %: N 3.22.

3,3-Dimethyl-6-trifluoromethyl-1-oxo-1,2,3,4-tetrahydroindolo[2,3-c]-quinoline (IIc). To a mixture of 3.8 g (0.05 mole) ammonium acetate and 50 ml of acetic acid we added 4.3 g (0.01 mole) of 3,3-dimethyl-6-trifluoromethyl-1,2,3,4-tetrahydroindolo[2,3-c]benzopyrylium and boiled the solution formed for 30 min. After cooling, 250 ml of water was added, and the precipitate formed was filtered and dried. Yield of IIc 3.2 g (95%), mp 157-158°C (from ethanol). Found, %: N 8.66. $C_{18}H_{15}F_3N_2O$. Calculated, %: N 8.43.

3,3-Dimethyl-6-ethyl-1-oxo-1,2,3,4-tetrahydroindolo[2,3-c]quinoline (IId). Gaseous ammonia was passed into a suspension of 3.9 g (0.01 mole) of 3,3-dimethyl-6-ethyl-1-oxo-1,2,3,4-tetrahydroindolo[2,3-c]benzopyrylium perchlorate in 50 ml of ether for 30 min. The solution was boiled for 30 min, cooled, and diluted with 250 ml of water. The precipitate formed was filtered, washed with water and dried. Yield of IId 2.6 g (88%), mp 140-142°C (from ethanol). Found, %: C 78.27; H 6.93; N 9.43. $C_{19}H_{20}N_2O$. Calculated, %: C 78.08; H 6.85; N 9.59.

Hydrochlorides of Compounds IIc and IId. The hydrochlorides were produced by adding the calculated amount of concentrated hydrochloric acid to their alcohol solutions. Hydrochloride of IIc: yield 95%, mp 226-227°C (from ethanol). Found, %: N 7.27. $C_{18}H_{15}F_3N_2O \cdot HCl$. Calculated, %: N 7.52. Hydrochloride of IId: yield 83%, mp 246-248°C (from ethanol). Found %: C 69.60; H 6.45; Cl 10.63; N 8.55. $C_{19}H_{20}N_2O \cdot HCl$. Calculated, %: C 69.41; H 6.39; Cl 10.81; N 8.53.

EXPERIMENTAL PHARMACOLOGICAL PART

In experiments on noninbred white rats weighing 200 ± 20 g, the number of consumptions of water and the number of approaches to the water dispenser were estimated under conditions of the method of a conflict situation [3] in groups of 8-12 animals which received intraperitoneal injections of water or of the test substances in doses of 1-10 mg/kg in a constant volume (1 ml). In experiments on mice weighing 20 ± 3 g, ED_{50} counteracting convulsions induced by subcutaneous injection of corazole (85 mg/kg) or picrotoxin (5 mg/kg), introduced immediately after intraperitoneal injection of the investigated substances, were determined. The sedative activity (ED_{50}) was determined according to the ability of the substances to decrease (by half or more) the number of horizontal movements; anesthesia-potentiating activity

was estimated by the dose (ED_{50}) of the substance against a background of which hexenal in a nonnarcotic dose (35 mg/kg intraperitoneally) induced a lateral position with a duration of no less than 5 min. ED_{50} and the error of the means were found by the method of probit-analysis according to V. P. Prozorovskii [6].

It was established that all the investigated compounds inhibit the spontaneous motor activity of the mice in doses constituting 1-8% of LD_{50} (Ic, d, IIb-d) or 12-18% of LD_{50} (Ia, b, e, IIa) (see Table 1). However, only some of them (Ia, c, d, IIc, d) potentiate hexenal anesthesia in doses constituting 20% or less of LD_{50}, while IIa, b, do not exhibit any ability to potentiate barbiturate anesthesia at all.

In sublethal and lethal doses all the substances (with the exception of IId) produce tremors in mice, especially pronounced in the anterior portion of the body, while harman (Ia) and a number of its derivatives (IIa, b) induce strong clonic convulsions. While exhibiting tremorogenic activity, IId counteracts the convulsive effect of picrotoxin but not of corazole. IId is an antagonist of both convulsive poisons.

Despite the presence of tremorogenic or convulsive action, Ia, b, d, IIc, as well as IId exhibit anxiolytic activity, substantially increasing the number of consumptions of water under conditions of the conflict situation method. The anxiolytic activity of harman and most of its derivatives is manifested at low doses. With increasing dose the anxiolytic effect disappears, and a number of substances (Ib, d, IId) have an anxiogenic effect when the doses are increased to 10 mg/kg, which finds expression in a decrease in the number of consumptions of water and/or approaches to the water dispenser under the conditions of the conflict situation method (see Table 1).

The anxiolytic activity of β-carboline derivatives is not correlated with their sedative, hexenal-potentiating, or anticonvulsive activity. It is detected for only part of the harman derivatives, although all of the investigated substances possess sedative activity, judging by their influence on spontaneous locomotion. Anxiolytic activity is absent in substances that have no hexenal potentiating effect (Ia, b), but it is also absent in a number of harmans capable of potentiating barbiturate anesthesia (Ic, e). Anxiolytic activity is characteristic of substances exhibiting anatgonism to picrotoxin (IIc), or picrotoxin and corazole (IId), but it is also detected in substances with tremorogenic (Id) and convulsive (Ia) activity.

It is suggested [12] that the anxiolytic activity of BD is associated with their influence on the benzodiazepine receptors, coupled with GABA receptors. Considering the ability of β-carbolines to interact with the latter and the presence of anxiolytic anxiogenic activity in harman and many of its derivatives (see Table 1), we might have considered harmans as partial agonists (agonists-antagonists) of the benzodiazepine receptors. However, the classic partial agonists exhibit the properties of agonists in low concentrations (doses), while in high concentrations they counteract their own effect. Harmans, on the contrary, have a benzodiazepine-like effect in low doses and exhibit anxiogenic properties of anti-benzodiazepines in high doses. The action of barbiturates is attributed to an influence on binding sites common to barbiturates and picrotoxin, coupled with the GABA receptors [12]. From Table 1 it is evident, however, that harman derivatives possessing pronounced hexenal-potentiating activity (Ia, c, d, IIc, d) do not necessarily exhibit antagonism to picrotoxin (Ia, c, d), as well as to corazole (Ia, c, d, IIc).

The aforementioned permits us to conclude that the anxiolytic and anxiogenic, hexenal-potentiating and anticonvulsive activities of harman derivatives are due to the participation of different mechanisms, independent to a substantial degree. This suggests the possibility of creating substances with anxiolytic activity on the basis of harmans that are virtually devoid of anxiogenic, hyptonic, and anticonvulsive properties.

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STRUCTURE AND ANTIMICROBIAL ACTIVITY OF 2-HYDROXY-CINNAMALDEHYDE DERIVATIVES

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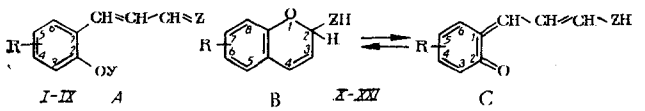
The establishment of the relationship between the structure of chemical compounds and their biological activity is one of the most urgent problems of modern chemical pharmacology. One of the approaches to the solution of this problem is to disclose a structural fragment common to a number of chemical compounds possessing the same type of biological activity.

In this work we studied the antimicrobial activity of 2-hydroxycinnamaldehyde derivatives I-XXI for the first time, and correlated the data obtained with their structure, which, in the crystalline state, as we have demonstrated earlier [1-4], is described by structures A, B, and C. The advisability of such an investigation is supported by the available literature data on the high antimicrobial activity of esters of 2-hydroxycinnamaldehyde isolated from natural products [6].



I: Y = H, Z = O; II: Y = Ac, Z = O; III: Y = H, Z = NPh; IV: Y = H, Z = NC_6H_4Br-p; V: Y = H, Z = $NC_6H_4NO_2$-p; VI: Y = Ac, Z = NPh; VII: R = 5,6-benzo, Z = NPh; VIII: R = 5,6-benzo, Z = O; IX: R = 5-Me, 3,4-benzo, Z = O; X: Z = O; XI: Z = NPh; XII: Z = NC_6H_4Br-p; XIII: Z = $NC_6H_4NO_2$-p; XIV: Z = NC_6H_4OMe-p; XV: Z = $NC_6H_4NO_2$-p; XVI: Z = O; XVII: Z = NCH_2Ph; XVIII: Z = NC_6H_4OMe-p. XIX: Z = NPh; XX: Z = NC_6H_4Br-p; XXI: R = 5,6-benzo, Z = NCH_2Ph; I — VI: R = H; VII — IX: Y = Ac; X — XIV: R = 5,6-benzo, XV, XVI: R = 6-Me, 7,8-benzo, XVIII — XX: R = 5-Me, 3,4-benzo

The structure of compounds I-XXI in solution depends on the polarity of the medium, the nature of the benzannelation, and the type of the substituent Z [1-4]. 2-Hydroxycinnamaldehyde I and its imines III-V exist in solvents of various polarities exclusively in a benzoid form, possessing an S-trans-E-configuration A [1], as a model of which their O-acetyl derivatives II and VI can serve. Benzannelated systems X-XXI have a cyclic 2H-chromene structure B in nonpolar solvents, while in polar media a ring-chain tautomeric equilibrium B $\rightleftarrows$ C of 2H-chromene (B) and o-quinoid (C) structures is realized for them, the position of which is

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