SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 1-R-2-[3'-R'-AMINO-2-HYDROXYPROPYL]-1,2,3,4-TETRAHYDRO-β-CARBOLINES

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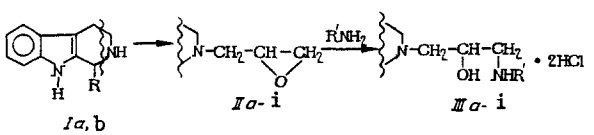
Many biologically active compounds which affect the central nervous and cardiovascular systems contain the heterocyclic indole or β-carboline fragment. It is believed that coupling these with the aminopropanol radical could extend the spectrum of such compounds, or increase their activity on the cardiovascular system [3]. We have therefore undertaken the synthesis of β-carbolines in which the 2-position is occupied by the aminopropanol residue.

The starting materials for the compounds (IIIa-i) were 1,2,3,4-tetrahydro-β-carboline (R = H) [10] and 1-methyl-1,2,3,4-tetrahydro-β-carboline (R = CH_3) [6].

Condensation of the β-carbolines (I) (R = H and CH_3) with epichorohydrin followed by treatment with sodium hydroxide solution gave the 2-epoxypropyl-1,2,3,4-tetrahydro-β-carbolines (II). Cleavage of the oxide ring was effected



Ia, b IIa-i IIIa-i

R=H(Ia, IIa-d, IIIa-d), CH_3 (Ib, IIe-i IIIe-i); R'= =s-Bu(IIIa, f), t-Bu(IIIb, g), $CH(CH_3)CH_2C_6H_5$ (IIIc, h), $CH(CH_3)CH_2CH_2C_6H_5$(IIId, i), $CH(CH_3)_2$(IIIe).

with primary amines, either under the usual conditions, or in sealed tubes. Elevated temperature resulted in resinification of some of the products, with a consequent reduction in the yields of the final products. Compounds (IIIa-i) were characterized as their dihydrochlorides, the IR spectra of which showed absorption at 3500-3200 (NH, OH assoc.) and 1620 and 1600 (C=C arom.) cm^{-1}. The mass spectrum showed the molecular ion and a number of characteristic fragments confirming the structure as (III) [4, 8].

EXPERIMENTAL (CHEMISTRY)

TLC was carried out on grade II alumina in the solvent system butanol–AcOH–water (20:1:3), developer iodine vapor. IR spectra were obtained on a UR-20 (East Germany) in Vaseline grease, and mass spectra on an MX-1303 with direct introduction of the sample into the ion source.

2-(2,3-Epoxypropyl)-1,2,3,4-tetrahydro-β-carboline (IIa-d). To a suspension of 4.7 g (27 mmole) of tetrahydro-β-carboline (Ia) in 20 ml of chloroform was added 2-3 drops of water and 2.55 g (27 mmole) of epichlorohydrin, and the mixture brought to the boil and stirred for 5-6 h at 52-55°C. Unreacted β-carboline was filtered off, the solvent distilled off, and the residual thick oil treated with 20-30 ml of 40° NaOH and stirred for 20-30 min at 40°C. The resulting solid was washed on the filter with cold water (100-150 ml) to give 3.1 g (50%) of (IIa), mp 155-157°C, $C_{14}H_{16}N_2O$. R_f 0.48.

1-Methyl-2-(2,3-epoxypropyl)-1,2,3,4-tetrahydro-β-carboline (IIe-i) was obtained as for (IIa-d), the solvent being dry ether and the reaction temperature 30-35°C. Yield 46.5%, mp 117°C. $C_{15}H_{18}N_2O$. R_f 0.50.

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TABLE 1. 1-R-2-(3'R'-Amino-2-hydroxypropyl)-1,2,3,4-tetrahydro-β-carboline Dihydrochlorides (IIIa-i)

Compound	Yield, %	mp, °C	Empirical formula	R_f rel.
a	21,3	144—145	$C_{18}H_{29}Cl_2N_3O$	0,46
b	20,0	230—231	$C_{18}H_{29}Cl_2N_3O$	0,45
c	31,8	174—175	$C_{23}H_{31}Cl_2N_3O$	0,43
d	22,0	134—135	$C_{24}H_{33}Cl_2N_3O$	0,43
e	64,8	176—177	$C_{18}H_{29}Cl_2N_3O$	0,43
f	35,5	146—147	$C_{19}H_{31}Cl_2N_3O$	0,40
g	50,0	186—187	$C_{19}H_{31}Cl_2N_3O$	0,44
h	53,3	164—165	$C_{24}H_{33}Cl_2N_3O$	0,45
i	16,4	170—171	$C_{25}H_{35}Cl_2N_3O$	0,47

1-R-2-(3-R'-Amino-2-hydroxypropyl)-1,2,3,4-tetrahydro-β-carboline Dihydrochlorides (IIIb, e, g). The epoxide (II) (10 mmole) in 30 ml of 2-propanol, 20 mmole of the appropriate amine, and 1-2 drops of water were heated in a sealed tube in an oil bath for 6-8 h at 120-140°C. Unreacted epoxide (II) was filtered off, and the 2-propanol and excess amine removed under reduced pressure. The oily residue was dissolved in dry THF, and treated with ethereal HCl to give the dihydrochloride (IIIb, e, g), which was recrystallized from alcohol-ether (1:10) (Table 1).

1-R-2-(3'-R'-Amino-2-hydroxypropyl)-1,2,3,4-tetrahydro-β-carboline Dihydrochlorides (IIIb, c, d, f, h, i). The epoxide (II) (10 mmole) in 40 ml of 2-propanol, 10 mmole of the appropriate amine, and 1-2 drops of water were boiled under reflux at 80°C for 10-12 h. Unreacted epoxide was filtered off, and the solvent removed. Excess high-boiling amines were removed by vacuum distillation. The residue was dissolved in dry THF, and ethereal HCl added to give the dihydrochloride, which was recrystallized from alcohol—ether (1:10) (Table 1). Mass spectrum of (IIIh), m/z (rel. I): 377(16), 215(20), 192(60), 185(28), 162(20), 91 (100).

EXPERIMENTAL (BIOLOGY)

The effects of (IIIa-i) on spontaneous motor activity, body temperature, and on the effects of apomorphine, phenamine (amphetamine), and hexenal were examined in mongrel white mice weighing 18-22 g and rats weighing 150-180 g of both sexes.

The compounds were administered in doses of 10 and 50 mg/kg intraperitoneally. Phenamine (5mg.kg) and hexenal (70 mg/kg) were given intraperitoneally 45 min after treatment with the test compound in a dose of 25 mg/kg, and apomorphine (2 mg/kg) after 30 min. The effects of the compounds on phenamine hypothermia and sterotypy, and on apormorphine hypothermia and stereotypy were assessed in mice 1, 2, 3, and 4 h after administration of the pharmacological "analyzers."

The acute LD_{50} values of (IIIg) and (IIIh) were determined in mice.

The effects of (IIIh) on brain serotonin and noradrenalin levels were measured in rats by ion exchange chromatography [5]. The compounds were administered intraperitoneally in a dose of 25 mg/kg one hour before decapitation.

The test results were evaluated statistically by the Student—Fisher and Litchfield—Wilcoxon methods.

Also examined was the antiarrhythmic activity of the compound in model "electrical" arrhythmia in cats [1]. The tests were carried out on 15 narcotized cats with artificial pulmonary ventilation. The electrical impulse was applied as rectangular impulses of duration 1 m/sec, frequency 20 Hz, from an ES-50-1 electronic stimulator.

The systemic arterial pressure (AP) was recorded in the common carotid artery. The indices of arrhythmia were sharp variations in the AP on stimulation with the electrical current, cardiac contraction by visual observation, and in some tests, the ECG (lead II). The compounds were administered into the femoral vein as the 1% aqueous solutions in doses of 1.3 and 5 mg/kg. The antiarrhythmic activity was assessed by the ability of the compounds to raise the excitation threshold, preventing the atrial flutter induced by electrical stimulation. The reference compounds used were quinidine and novocainamid.

The effects of (IIIa-i) in a final concentration of 0.05 mM on α-adreno-receptors and on the transmission of excitation in the sympathetic nerve endings were examined in isolated rat vas deferens [2].

In experiments on rats, all the compounds in a dose of 50 mg/kg reduced the skin temperature by 1-2°C for 1 h, and suppressed the motor activity of animals induced by lateral positioning. In mice, a dose of 50 mg/kg of (IIId) resulted in the development of clonic-tonic convulsions resulting in the deaths of 40% of the animals. Compounds (IIIg) and (IIIh) suppressed motor activity to the extent of one point, assessed as in [7], as well as hypothermia, increasing with increased doses. The greatest hypothermic effect was obtained with (IIIg), which reduced the temperature of mice by 5.7°C one hour after administration of a dose of 50 mg/kg. In addition, narrrowing of the eyelid slit by 25% (measured as in [9]) was seen.

Compounds (IIId, g, h) prevented the development of amphetamine hyperthermia in mice for 30 min after treatment, without affecting sterotypic nodding. These compounds eliminated the aggression and circular movements which normally develop following administration of amphetamine. These compounds also enhanced apomorphine hypothermia by 3.5-3.9°C for 1 h without affecting apomorphine stereotypy. They also shortened hexenal sleep by 50-60% ($P < 0.05$).

When given to rats in a dose of 25 mg/kg, (IIIg) increased the serotonin and noradrenalin levels by 33 and 44% respectively one hour after administration.

The LD_{50} of (IIIg) in mice was 56 (43.7-71.7) mg/kg, and of (IIIh) 80 (70.8-90.4) mg/kg.

Tests on cats showed that from a dose of 3 mg/kg (IIIe) and (IIIh) prevented arrhythmia resulting from electrical stimulation of the right auricle of the heart, this effect lasting for 5-10 min. Increasing the dose to 5 mg/kg resulted in the effect appearing late (after 5-7 min), and lasting for 15-20 min. Sensitivity to electrical stimulation (the excitation threshold) was restored only when the voltage was doubled.

Compounds (IIIb) and (IIIf) showed weak and short-lived antiarrhythmic activity, and the remainder were of low activity.

Compounds (IIIa, d, h, i) blocked the adrenoreceptors of the rat vas deferens by 30-40%, and moderately retarded the conduction of excitation through the sympathetic nerve fibers, but the remaining compounds did not show any appreciable activity in this respect.

Of the compounds examined, therefore, the tert-butylamino- (IIIg) and the phenylpropylamino-derivative (IIIh) of tetrahydro-β-carboline, like neuroleptics, suppressed motor activity in mice and rats, caused blepharoptosis and hypothermia, and counteracted amphetamine hyperthermia. Unlike the known neuroleptics, the compounds did not block sterotypic forms of behavior resulting from treatment with amphetamine or apomorphine.

Like the monoamine oxidase inhibitors, these compounds enhanced apomorphine hypothermia, and counteracted the sedative effects of hexenal. The most active compound, the tert-butylamino derivative of carboline (IIIg), increased the serotonin and noradrenalin levels in rat brain. The most active compounds were, however, much more toxic thant the known psychotropic drugs.

In model auricular forms of arrhythmia, the isopropylamino (IIIe) and tert-butylamino (IIIg) β-carbolines displayed moderate antiarrhythmic activity, but in duration and levels of activity they were inferior to quinidine and novocainamid.

The test compounds showed weak α- and β-adrenolytic and sympatholytic activity.

These compounds have therefore shown moderate activity in pharmacological tests.

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SYNTHESIS AND INOTROPIC ACTIVITY OF N,N'-DI-[2,6-DIMETHYL-4-(2,3,5,6-TETRAHYDRO-6-PHENYLIMIDAZO[2,1-b]THIAZOLIO-7-YL)METHYL] DIPHENYLCARBODIIMIDE DIBROMIDE

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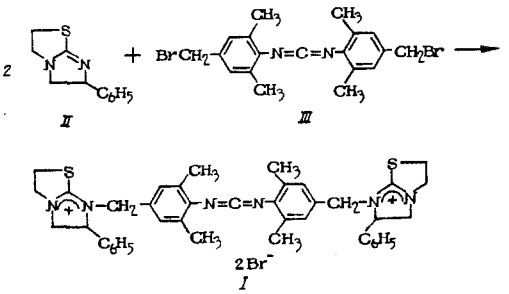
The identification and study of nontraditional cardiotonic compounds is a matter of urgency in contemporary pharmacology and pharmacy [2]. Pyrimidines, imidazoles, phthalazines, polypeptides, and arylalkylamines are known which possess positive inotropic activity [1, 3, 4]. Cardiotonic activity has also been found in some condensed imidazothiazoles [1]. High pharmacological activity has been found in bisquaternary ammonium salts, including some with hydrophobic bridging groups [1]. With this in mind, it was of interest to use bridging fragments of a fixed chain length and linear structure, such as carbodiimides, which also have physiological activity [5, 6]. It was therefore desired to synthesize novel chemical compounds containing both types of pharmacophoric fragments.

The approach which we adopted to the construction of such compounds



resulted in the formation of the salt-like carbodiimide (I), and consisted in the ready alkylation of 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]thiazole (II) with N,N'-2,2',6,6'-tetramethyl-4,4'-dibromomethyldiphenylcarbodiimide (III).

The carbodiimide (I) was a colorless, crystalline solid which was readily soluble in water and highly polar organic solvents. Its purity was confirmed by TLC, its composition by elemental analysis, and its structure by its IR spectrum, which showed strong absorption for the carbodiimide group at 2170 cm^{-1}.

EXPERIMENTAL (CHEMISTRY)

The IR spectrum was obtained on a UR-20 instrument (East Germany) in a KBr disk. TLC was carried out on Silufol UV-254 plates (Czech SSR).

N,N'-Di-[2,6-dimethyl-4-(2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]-thiazolio-7-yl)methyl]-diphenylcarbodiimide Dibromide (I). To a solution of 0.86 g (0.002 mole) of the carbodiimide (III) in 15 ml of chloroform was added 0.82 g (0.004 mole) of the thiazole (II) in 10 ml of chloroform. The mixture was kept for 48 h, then the solvent was evaporated, and the residue treated with 20 ml of diethyl ether and kept for 24 h. The crystalline product was filtered off to give 1.54 g (91%) of (I), mp 65-67°C. $C_{41}H_{46}Br_2N_6S_2$.

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