EXPERIMENTAL (BIOLOGY)

To determine the biological activity of the compounds, the yeast Saccharomyces cerevisiae (Krasnodar strain) was used. Before the test, the culture was activated by transferring from wort agar to a sterile nutrient medium containing 3 g $(NH_4)_2SO_4$, 2.5 g KH_2PO_4, 1 g $MgSO_4 \cdot 7H_2O$, wort 50 ml, and sucrose 20 g in 1 liter of distilled water. For synchronization, the yeast was decanted for 24 h with a sterile vitamin-free medium containing only the major elements of the basic nutrient medium used in the tests. The basic medium contained 3 g $(NH_4)_2SO_4$, 2.5 g KH_2PO_4, 1 g $MgSO_4 \cdot 7H_2O$, 0.850 mg $FeSO_4 \cdot 7H_2O$, 1 g asparagine, 4 mg thiamine, 10 mg inositol, 1 mg pyridoxine, 2 μg biotin, sucrose 20 g, and distilled water to 1 liter. The nutrient media were sterilized at 1 atm for 20 min. Asparagine and sucrose solutions were sterilized separately under the same conditions, and combined with the medium before the test. The complexes were tested in concentrations equimolar to 0.5 mole of calcium D-pantothenate, dissolved in sterile distilled water.

The vitamin activity of the compounds was assessed by the extent of growth of the yeast in micrograms per 1 ml of dry weight after 24 h at 30°C, as measured turbidimetrically on an FÉK-56-B-M photoelectric colorimeter with a red filter. Each test was repeated five times.

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PHARMACOLOGICAL ACTIVITY OF URACYL AND ADAMANTYL DERIVATIVES OF β-PHENYLISOPROPYLAMINE

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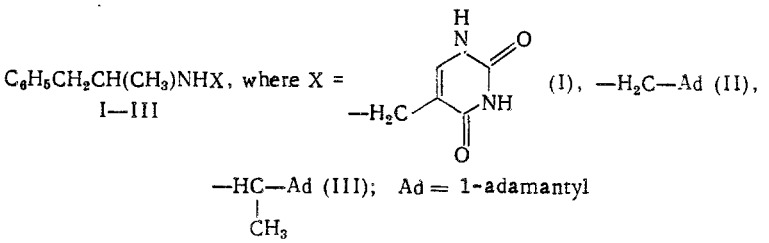
We have previously synthesized [1] some derivatives of phenamine (amphetamine) which possess sedative and central adrenolytic activity [2], and which show other pharmacological effects. Continuing a search for pharmacologically active derivatives of β-phenylisopropylamine, we have synthesized N-(5-uracyl)methyl-2-phenylisopropylamine (I), N-(1-adamantylmethyl)-2-phenylisopropylamine (II), and N-[1-(1-adamantyl)ethyl]-2-phenylisopropylamine, and examined the pharmacological properties of these compounds



Compound (I) was obtained by the reaction between 5-chloromethyluracil and 2-phenylisopropylamine. The 5-chloromethyluracil required for this reaction was obtained as described in the literature [4].

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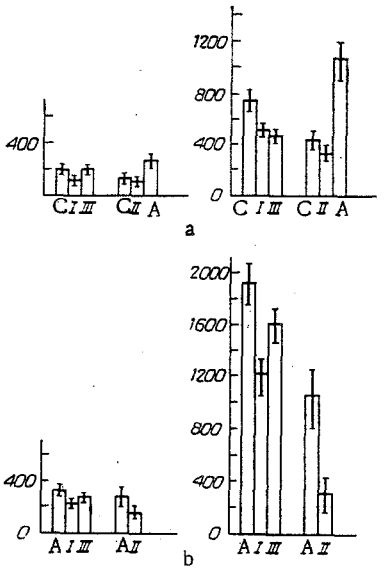

Fig. 1. Effect of β-phenylisopropylamine derivatives on spontaneous motor activity (a) and hyperactivity induced by amphetamine (b). Horizontal axis, compound: C is the control (physiological saline); I is compound (I) (30 mg/kg); II is (II), (5 mg/kg); A is amphetamine (5 mg/kg). The vertical axis shows the number of movements in 5 min (on the left) and in 30 min (on the right).

Compounds (II) and (III) were synthesized by the Leuckart-Wallach reaction from 1-aminomethyladamantane and 1-(1-adamantyl)ethylamine, respectively, and methyl benzyl ketone. Attempts to obtain (II) by reducing adamantane-1-carboxylic acid 2-phenylisopropylamide were unsuccessful, the amide being recovered unchanged. The reducing agents tried were lithium aluminohydride in tetrahydrofuran and sodium bis(2-methoxyethoxy)dihydroaluminate. Clearly, steric hindrance is responsible for the lack of reaction.

Compounds (I) and (II) as the hydrochlorides, and (III) as the phosphate (in view of the low solubility of the hydrochloride in water) were subjected to pharmacological studies. The pharmacological tests were as follows: determination of toxicity (LD_{50}), examination of effects on the duration of the sedative effects of hexobarbitone, effects on orientational and spontaneous motor activity, and on motor hyperactivity induced by amphetamine. Amphetamine is known to have an activating effect on the secretion of ACTH glucocorticoids [5], and therefore the effects of the compounds on the activity of the hypophyseal-adrenal system were examined.

EXPERIMENTAL (CHEMISTRY)

N-(5-Uracyl)methyl-2-phenylisopropylamine Hydrochloride (I). 5-Chloromethyluracil (3.17 g) was dissolved with stirring and heating in 80 ml of dioxane. The solution was cooled to room temperature, and 5.7 ml of 2-phenylisopropylamine in 20 ml of dioxane added dropwise. The reaction mixture was stirred and heated for 8 h, and kept overnight. The solid was filtered off, washed repeatedly with dioxane, and dried in air, to give 4 g of product. To this solid were added 300 ml of water and 2.5 ml of conc. HCl, the mixture boiled, the hot solution filtered, and the filtrate evaporated under reduced pressure to dryness. Yield of (I) hydrochloride 56%, mp 250-255°C (decomp.). Found, %: N 14.17, 14.26; Cl 11.47, 11.49. $C_{14}H_{18}ClN_3O_2$. Calculated, %: N 14.21; Cl 11.90.

N-(-Adamantylmethyl)-2-phenylisopropylamine (II) Hydrochloride. In a Claisen flask fitted with two thermometers (one reaching to the bottom of the flask) and a condenser for distillation was placed 30 ml of formic acid, and 1-adamantylamine (5 g) added cautiously with cooling (ice bath). The water–formic acid azeotrope was distilled off at 103-107°C. The mixture was cooled, and 5.58 g of methylbenzyl ketone added, and the temperature was then slowly raised over 5 h to 180°C, and kept at this temperature for 8 h. The mixture was cooled, the condenser for distillation replaced by a reflux condenser, 3 ml of conc. HCl was

TABLE 1. Effects of β-Phenylisopropylamine Derivatives on the Time of Induction and the Duration of Narcotic Sleep in Mice Induced by Hexobarbitone

Compound	Toxicity, LD_{50}, mg/kg	Dose, mg/kg	Time of induction of sleep, min	Duration of sleep, min
Hexobarbitone (control)	—	100	5,1±0,3	92,6±6,1
I	645	30	2,2±0,1*	87,1±9,7
III	230	20	1,5±0,1*	85,1±8,1
Hexobarbitone (control)	—	100	9,1±1,2	26,8±3,1
II	93,7	5	4,5±0,4*	33,3±4,6

Note. Ten rats were used per group. An asterisk indicates $P < 0.05$.

TABLE 2. Effects of β-Phenylisopropylamine Derivatives on Blood Plasma Factors (M ± m)

Compound	Dose, mg/kg	11-HCC, μg %	Free fatty acids, meq/liter	Glucose, mg%
Control		16,5±1,3	367,7±40,5	107,6±3,7
I	5	11,1±2,0	483,9±58,8	115,1±4,5
	20	25,9±3,1*	838,9±98,8*	118,9±4,6
II	5	24,1±2,3*	483,7±27,5*	107,7±4,0
	20	43,3±1,2*	442,0±26,3	112,1±3,2
III	5	21,6±1,5	383,9±51,8	105,2±2,5
	20	38,2±3,2*	538,9±43,2*	102,5±1,8

added, and boiled for 6 h. The mixture was then dissolved in ethanol and distilled in steam. The residual solution was decanted into a beaker, and kept in the refrigerator overnight. The solid (II) hydrochloride was filtered off and air-dried to give 44% yield, mp 303-305°C (ethanol–water). Found, %: C 74.80, 74.94; H 8.88, 9.12; Cl 10.88, 10.68; N 4.46, 4.48. $C_{20}H_{31}ClN$. Calculated, %: C 75.05; H 9.45; Cl 11.08; N 4.38.

N-[1-Adamantyl)ethyl]-2-phenylisopropylamine (III) Hydrochloride. Obtained as for (II). (III) Hydrochloride was isolated as follows: After boiling the reaction mixture with concentrated HCl, the resulting solid was dissolved in water, filtered from unreacted 1-adamantylethylamine, and the filtrate boiled with charcoal. The water was distilled off, and the residue recrystallized from water and ethanol to give a 50% yield calculated or adamantylethylamine reacted, mp 278-279°C. C 75.10, 75.14; H 9.43, 9.91; Cl 10.70, 10.67; N 3.93, 3.86. $C_{21}H_{33}ClN$. Calculated, %: C 75.30; H 9.93; Cl 10.59; N 4.18.

N[1-(1-Adamantyl)ethyl]-2-phenylisopropylamine Phosphate. (III) Hydrochloride (3 g) was dissolved in 10 ml of 1 N NaOH, and the free base which separated was extracted with chloroform, dried over $MgSO_4$, and the chloroform distilled off to dryness. To the resulting oily residue was added an equivalent amount of dilute H_3PO_4 (1:3). After 24 h, the water was distilled off and the residue washed with dry ether to give (III) phosphate as a glassy solid.

Adamantane-1-carboxylic Acid 2-Phenylisopropylamide. Adamantanecarboxylic acid (7.5 g) was boiled with 30 ml of thionyl chloride in a flask fitted with a reflux condenser for 2 h. Excess thionyl chloride was distilled off, and the residue treated with 15 ml of dry benzene, which was again distilled off. The procedure was repeated. The resulting adamantanecarbonyl chloride was transferred to a flask fitted with a stirrer, reflux condenser, and a dropping funnel. It was dissolved in 15 ml of dry benzene, cooled, and treated dropwise with stirring and cooling with a mixture of 5.9 ml of 2-phenylisopropylamine and 9 ml of triethylamine in 30 ml of dry benzene. The mixture was kept overnight, and the solid filtered off and washed with water to remove triethylamine hydrochloride. The benzene was evaporated to dryness, and the residue combined with the main product. Crystallization from aqueous alcohol gave 81.2% of product, mp 148-149°C. Found, %: C 80.83, 80.81; H 8.80, 8.60. $C_{20}H_{27}NO$. Calculated, %: C 80.76; H 9.15.

The IR spectrum was obtained in vaseline oil on an IKS-28 spectrophotometer, ν_{CO} 1628, 1546 cm^{-1}.

Reduction of Adamantane-1-carboxylic Acid 2-Phenylisopropylamide. To 2.6 g of lithium aluminohydride in 70 ml of THF was added dropwise 9.67 g of adamantane-1-carboxylic acid 2-phenylisopropylamide in 90 ml of THF, and the mixture boiled for 12 h. The mixture was then decomposed with cooling with 30 ml of water, and the solid filtered off and washed with ether and chloroform. The solvent was removed nearly to dryness, and the residual solid filtered off and dried. mp 147-148°C, weight 9.5 g. The solid was insoluble in dilute HCl, and its IR spectrum was identical with that of the original amide.

EXPERIMENTAL (PHARMACOLOGY)

The tests were carried out in male white mice weighing 20-25 g. Acute toxicities (LD_{50}) were determined by Behren's method by the intraperitoneal route. The effects of the test compounds on the sedative effects of hexobarbitone were assessed from the time of onset and the duration of the adoption of a lateral position by the mice. The test compounds were administered intraperitoneally in a dose of 1/15 of the LD_{50} 20 min prior to the injection of hexobarbitone (100 mg/kg). Motor activity was measured in a DAÉR-20 apparatus for 30 min, the test compounds being administered 20 min before the test. The effects of the compounds on motor hyperactivity induced by amphetamine (5 mg/kg) were assessed under similar conditions. The results were treated statistically, using the Student criterion for $p = 0.05$. The test results are shown in Table 1 and Fig. 1.

The activity of the hypophyseal–adrenocortical system was assessed by the content of 11-hydroxycorticosteroids (11-HCC) in the peripheral blood plasma, the concentration being measured by fluorimetry as described in [3], using a Krasnogvardeets fluorimeter produced by the BIAN plant. The test results are shown in Table 2.

The test results showed that the compounds accelerated the onset of hexobarbitone sleep, but had no effect on its duration. All three compounds, but especially (I) and (III), decreased spontaneous motor activity. Compound (II) showed marked antagonism to amphetamine, suppressing the motor hyperactivity induced by it.

As will be seen from Table 2, all the compounds had a stimulant effect on the hypophyseal–adrenocortical system, as shown by the greater amounts of corticosteroids present in the blood plasma as compared with the controls. In parallel with the increase in corticosteroid concentrations, the level of free (nonesterified) fatty acids rose, indicating enhanced lipolysis as a result of the activation of the hypophyseal–adrenal system. The blood glucose levels remained largely unchanged.

These results show that these compounds have a depressant effect on the CNS, but they retain a stimulant effect on the hypophyseal–adrenal system similar to that of amphetamine.

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