BENZOFURAN-2-CARBOXYLIC ACID DERIVATIVES AND THEIR ACTION ON THE CENTRAL NERVOUS SYSTEM

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Continuing our search for pharmacologically active compounds among substituted benzofuran-2-carboxylic acids, particularly substances that have an effect on the central nervous system, we have obtained some amides and esters (I-XIII, Table 1). 3-Methyl-6,7-dimethoxy- and 3-methyl-6,7-diethoxybenzofuran-2-carboxylic acids were nitrated (with 72% nitric acid in acetic acid at ~20°). The nitro group probably occupies the 5-position of the benzofuran ring. VIII was converted to the corresponding amino derivative by catalytic hydrogenation.

The effect of the compounds obtained on the central nervous system was investigated by means of widely used screening methods: intensification of the action of narcotic substances (thiopental sodium) on mice, the ability to induce catalepsy in rats, analgesic action on mice (Haffner method), and the determination of the toxicity of the substances in mice.

It was established that all of the substances have a depressive effect on the central nervous system; the duration of the action of the substances is 30-40 min. The degree of activity of the compounds depends on their chemical structure. The investigated substances can arbitrarily be divided into three groups. In the first group of compounds, two methoxy groups in the benzofuran ring are situated in the 5- and 6-positions. For II, ED_{50} with respect to the action on a subthreshold dose of thiopental sodium is 21 mg/kg, while LD_{50} is 160 mg/kg. This compound does not have cataleptic and analgesic action. Replacement of the piperazine residue by a dimethylaminoethoxy group (compound I) reduces the activity with respect to the ability to raise the action of thiopental sodium (ED_{50} = 40 mg/kg). The toxicity changes slightly (LD_{50} = 180 mg/kg), and cataleptic and analgesic action is absent.

The second group contains compounds with two methoxy groups in the 6- and 7-positions. IX, the isomer of II, has more pronounced activity with respect to the ability to raise the action of thiopental sodium (ED_{50} = 16 mg/kg) and manifests cataleptic action (ED_{50} = 24 mg/kg) and a toxicity of LD_{50} = 210 mg/kg. The activity and toxicity of I and III with respect to these tests were approximately the same. The most active of all the compounds is VII with respect to its ability to raise the action of thiopental sodium (ED_{50} = 11 mg/kg) and with respect to cataleptic action (ED_{50} = 16 mg/kg). VII has analgesic action (ED_{50} = 95 mg/kg). The toxicity of VII is one third that of the substances named above (LD_{50} = 600 mg/kg). V, VI, and X raise the action of thiopental sodium (ED_{50} = 30-90 mg/kg) and induce catalepsy in doses of 75-140 mg/kg with LD_{50} = 600 mg/kg. These compounds do not induce analgesia.

The introduction of a nitro group into VII led to a sharp decrease in activity with respect to all of the indexes: the ability to raise the action of thiopental sodium was ED_{50} = 60 mg/kg (LD_{50} > 1000 mg/kg), and cataleptic and analgesic action was absent. The replacement of a nitro group by an amino group did not change the activity of the substance. The least active substance was IV. It does not raise the action of thiopental sodium and does not induce catalepsy (LD_{50} > 1000 mg/kg).

In the third group of compounds, two methoxy groups in the 6- and 7-positions are replaced by ethoxy groups. XIII is of slight activity with respect to raising the action of thiopental sodium (ED_{50} = 90 mg/kg),

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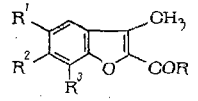
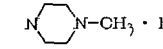
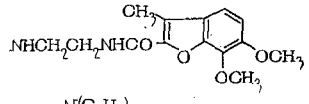
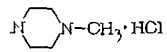
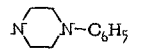
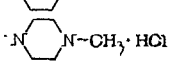
TABLE 1. Benzofuran-2-carboxylic Acid Derivatives 

Compound	R	R^1	R^2	R^3	Yield (%)	mp [5]	Found (%)				Empirical formula	Calculated (%)			
							C	H	Cl	N		C	H	Cl	N
I	$OCH_2CH_2N(CH_3)_2 \cdot HCl$	OCH_3	OCH_3	H	49	225—6 (dec.)	56,08	6,40	10,12	4,10	$C_{15}H_{22}ClNO_5$	55,90	6,45	10,32	4,07
II		OCH_3	OCH_3	H	77	259—60 (dec.)	57,70	6,45	9,77	7,86	$C_{17}H_{23}ClN_2O_4$	57,54	6,53	9,99	7,89
III	$OCH_2CH_2N(CH_3)_2 \cdot HCl$	H	OCH_3	OCH_3	63	205—6 (dec.)	55,84	6,49	10,02	4,07	$C_{16}H_{22}ClNO_5$	55,90	6,45	10,32	4,07
IV[1]		H	OCH_3	OCH_3	76	250—1 (dec.)	62,77	5,73	—	5,63	$C_{26}H_{28}N_2O_8$	62,91	5,68	—	5,64
V	$N(C_2H_5)_2$	H	OCH_3	OCH_3	93	72—3	66,05	7,16	—	4,82	$C_{16}H_{21}NO_4$	65,97	7,27	—	4,81
VI[2]	$N(CH_2CH_2OH)_2$	H	OCH_3	OCH_3	24	85—6	59,39	6,46	—	4,60	$C_{16}H_{21}NO_6$	59,44	6,55	—	4,33
VII		H	OCH_3	OCH_3	68	79,5—80	63,05	6,30	—	4,64	$C_{16}H_{19}NO_5$	62,95	6,27	—	4,59
VIII[3]		NO_2	OCH_3	OCH_3	88	189—90	54,86	5,09	—	7,95	$C_{16}H_{18}N_2O_7$	54,86	5,18	—	8,00
IX		H	OCH_3	OCH_3	89	261—62 (dec.)	57,45	6,37	9,96	7,86	$C_{17}H_{23}ClN_2O_4$	57,54	6,53	9,99	7,89
X		H	OCH_3	OCH_3	84	150—50,5	69,36	6,33	—	7,30	$C_{22}H_{24}N_2O_4$	69,44	6,36	—	7,37
XI		H	OC_2H_5	OC_2H_5	78	104—5	64,75	7,10	—	4,30	$C_{18}H_{23}NO_5$	64,83	6,95	—	4,20
XII[4]		NO_2	OC_2H_5	OC_2H_5	81	150—1	57,10	5,91	—	7,44	$C_{18}H_{22}N_2O_7$	57,14	5,86	—	7,41
XIII		H	OC_2H_5	OC_2H_5	73	217—8 (dec.)	59,99	7,09	9,19	7,80	$C_{19}H_{27}ClN_2O_4$	59,60	7,11	9,26	7,32

[1]After ~16 h, the compound was filtered, washed with alcohol, water, and again with alcohol.

[2]After ~16 h, the reaction mass was extracted with a small amount of water. The dichloroethane solution was dried with magnesium sulfate and filtered. The solvent was removed by distillation, and the residue was treated with ether.

[3]A 45-ml sample of thionyl chloride was taken for the experiment with refluxing for 1.5 h. The acid chloride was dissolved with slight heating in 150 ml of dichloroethane, and morpholine in 10 ml of dichloroethane was then added to it, at ~20°.

[4]A 45-ml sample of thionyl chloride was used with refluxing for 1.5 h.

[5]I and IV were crystallized from butanol; VIII, X, and XII were crystallized from alcohol; II, III, IX, and XIII were crystallized from absolute alcohol; V and XI were crystallized from neutral ether; VI was crystallized from benzene; and VII was crystallized from benzene containing petroleum ether.

and no cataleptic action was observed (LD_{50} = 250 mg/kg). Replacement of the piperazine residue in XIII by a morpholine group intensifies the activity: ED_{50} = 45 mg/kg for XI with respect to raising the action of thiopental sodium, cataleptic action was manifested (ED_{50} = 100 mg/kg), and the toxicity was reduced (LD_{50} = 1200 mg/kg). The introduction of a nitro group into XI weakens the activity (ED_{50} = 100 mg/kg, with respect to raising the action of thiopental sodium), the ability to induce catalepsy vanishes, and the toxicity is sharply reduced (LD_{50} = 1500 mg/kg).

As a result of our experiments, it can be concluded that the most active compounds are those in the second group. The introduction of nitro and amino groups into the benzene ring weakens the activity of the compounds. Of the derivatives involving the carboxyl group, the most active substances proved to be compounds with a morpholine residue.

EXPERIMENTAL

4-Methyl-7,8-diethoxycoumarin. A suspension of 19.2 g of 4-methyl-7,8-dihydroxycoumarin, 46.8 g of ethyl iodide, and 41.4 g of anhydrous potassium carbonate in 200 ml of acetone was refluxed on a water bath for 25 h. The solvent was removed by distillation, and the residue was treated with 5% sodium hydroxide and chloroform until the residue dissolved. The organic layer was separated, and the aqueous layer was additionally extracted with chloroform. The combined chloroform extracts were washed with water and dried. The solvent was removed by distillation, the residue was treated with petroleum ether, and the crystallized substance was filtered to give 13 g (52%) of a product with mp 65-66° (from benzene with petroleum ether). Found, %: C 67.78; H 16.61. $C_{14}H_{16}O_4$. Calculated, %: C 67.72; H 6.50.

3-Bromo-4-methyl-7,8-diethoxycoumarin. A solution of 2.4 g of bromine in 5 ml of chloroform was added dropwise with stirring at 20° to a solution of 7.45 g of 4-methyl-7,8-diethoxycoumarin in 50 ml of chloroform. A precipitate formed initially and redissolved after stirring for 1 h. The next day, the solvent was removed by distillation, and the residue was recrystallized from alcohol to give 7.21 g (73%) of a product with mp 130.5-131.5° (from alcohol). Found, %: C 51.43; H 4.67; Br 24.60. $C_{14}H_{15}BrO_4$. Calculated, %: C 51.40; H 4.62; Br 24.42.

3-Methyl-6,7-diethoxybenzofuran-2-carboxylic Acid. A solution of 3.27 g of 3-bromo-4-methyl-7,8-diethoxycoumarin and 3.36 g of potassium hydroxide in 40 ml of alcohol was refluxed for 1.5 h. The alcohol was removed by distillation, and the residue was dissolved in water. The solution was filtered, and 2.56 g (97%) of acid with mp 204-205° (dec., from alcohol) was isolated from the filtrate by acidification with dilute hydrochloric acid. Found, %: C 63.68; H 6.05. $C_{14}H_{16}O_5$. Calculated, %: C 63.62; H 6.10.

3-Methyl-5-nitro-6,7-dimethoxybenzofuran-2-carboxylic Acid. A 1.18-g sample of 3-methyl-6,7-dimethoxybenzofuran-2-carboxylic acid was dissolved with slight heating in 20 ml of acetic acid, the solution was cooled to ~ 20°, and 0.31 ml of 72% nitric acid in 10 ml of acetic acid was added dropwise with stirring. The mixture was stirred for 20 min, and the resulting precipitate was filtered and washed with acetic acid, alcohol, and ether to give 1 g (71%) of a product with mp 273-274° (dec., from alcohol). Found, %: C 51.21; H 4.06; N 4.88. $C_{12}H_{11}NO_7$. Calculated, %: C 51.25; H 3.94; N 4.98.

3-Methyl-5-nitro-6,7-diethoxybenzofuran-2-carboxylic Acid. This was similarly obtained in 68% yield (50 ml of acetic acid was used for 0.005 mole of starting material) and had mp 257-258° (dec., from alcohol). Found, %: C 54.37; H 4.82; N 4.68. $C_{14}H_{15}NO_7$. Calculated, %: C 54.37; H 4.89; N 4.53.

3-Methyl-5-amino-6,7-dimethoxybenzofuran-2-carboxylic Acid Morpholide. A freshly prepared suspension of 0.87 g of 3-methyl-5-nitro-6,7-dimethoxybenzofuran-2-carboxylic acid morpholide in 100 ml of alcohol (obtained on cooling a boiling alcohol solution to 40°) was added to 0.3 g of reduced 2.5% $PdO/BaSO_4$ in 30 ml of alcohol, and the compound was hydrogenated with stirring under the usual conditions until the theoretical amount of hydrogen had been absorbed. The filtrate was evaporated to dryness, and the residue was recrystallized from benzene to give 0.5 g (63%) of a product with mp 173-174° (from benzene). Found, %: C 59.69; H 6.25; N 8.91. $C_{16}H_{20}N_2O_5$. Calculated, %: C 60.01; H 6.29; N 8.75.

Method for the Preparation of I-XIII. A 0.015-mole sample of the appropriate acid and 30 ml of thionyl chloride was removed by vacuum distillation, and the residue was diluted to three times its original volume with absolute benzene. A 0.03 mole sample of the amine (in the preparation of IV-VIII and X-XII) in 10 ml of dichloroethane was added dropwise with stirring at 0-5° to the precipitate dissolved in 80 ml of anhydrous dichloroethane, and the mixture was allowed to stand at room temperature until the next day. The mixture was filtered away from the insoluble residue, the filtrate was vacuum-evaporated, and the residue was dis-

solved in absolute benzene. The solution was filtered to remove traces of amine hydrochloride, and the filtrate was evaporated. The residue was recrystallized, and the compounds were dried in vacuo over phosphorus pentoxide. Equimolar amounts of acid and amine were used to obtain the hydrochlorides of I-III, IX, and XIII. The resulting precipitate of the hydrochloride of the target product was filtered the next day, washed with dichloroethane and ether, recrystallized, and dried in vacuo at 80° over phosphorus pentoxide for 2 h.