(3:2). IR frequencies, in cm^{-1}, as follows: ν_{CO}, 1720-1730 for the isopropyl ethers, 1710-1720 for the alkyl ethers; ν_{NH}, 3260-3270, 3370, and 3350-3360.

The previously described [3] compound VII was prepared similarly.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF AMIDES OF ω-(PHTHALIMIDO)-ALKYL CARBOXYLIC ACIDS

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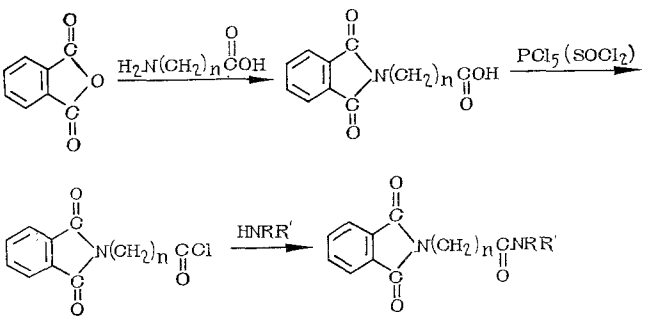
UDC 615.213:547.584].012.1

It is known that many carboxylic acid amides have anticonvulsant activity (ACA). For example, N-benzyl-β-chloropropionamide (chloracon), N-phenylethyl-β-chloropropionamide (fenacon), carbamazepine, methinedione, etc., are anticonvulsant and antitremor preparations. Amides of benzilic, mandelic, and diphenylacetic acids also have anticonvulsant properties [1-3]. Amides which have a phthalimide group in their make-up exert a depressing action on the central nervous system. For example, α-phthalimidobutyramide exerts an anticonvulsive action [4]; α,α-dialkyl-α-phthalimidoacetamides, an anticonvulsive and anesthetizing action [5, 6].

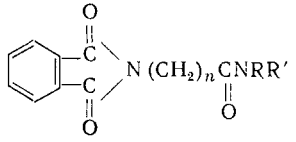
With the objective of seeking new compounds having higher biological activity, and to study the dependence between chemical structure and biological activity, we have synthesized a series of amides of phthalimidoacetic and γ-phthalimidobutyric acids by the following scheme:



I-XIX

Perm' Pharmaceutical Institute. Translated from Khimio-Farmatsevticheskii Zhurnal, No. 2, pp. 25-30, February, 1980. Original article submitted July 30, 1979.

TABLE 1. Physicochemical Properties of Amides of Phthalimidocarboxylic Acids



Compound	n	R	R′	Yield, %	m.p., °C	Found, %			Empirical formula	Calculated, %		
						C	H	N		C	H	N
I	1	H	H	82	259—60	58,93	3,78	13,90	$C_{10}H_8N_2O_3$	58,87	3,96	13,72
II	1	H	CH_3	83	248—50	60,65	4,83	12,79	$C_{11}H_{10}N_2O_3$	60,55	4,63	12,84
III	1	H	C_2H_5	79	227—9	61,89	5,00	12,18	$C_{12}H_{12}N_2O_3$	62,05	5,22	12,06
IV	1	H	C_3H_7	87	186—8	63,27	5,69	11,44	$C_{13}H_{14}N_2O_3$	63,41	5,73	11,34
V	1	H	C_4H_9	91	194—6	64,40	6,29	10,91	$C_{14}H_{16}N_2O_3$	64,59	6,21	10,77
VI	1	H	$CH_2CH\text{-}CH_2$	81	180—2	63,78	4,79	11,69	$C_{13}H_{12}N_2O_3$	63,91	4,94	11,47
VII	1	H	C_6H_5	85	231—2	68,66	4,29	10,11	$C_{16}H_{12}N_2O_3$	68,57	4,32	10,00
VIII	1	C_2H_5	C_2H_5	93	148—50	64,50	6,05	10,58	$C_{14}H_{16}N_2O_3$	64,59	6,21	10,77
IX	1	C_6H_5	C_6H_5	76	181—3	73,96	4,40	7,75	$C_{22}H_{16}N_2O_3$	74,15	4,53	7,86
X	3	H	H	75	165—7	61,96	5,09	12,02	$C_{12}H_{12}N_2O_3$	62,05	5,22	12,06
XI	3	H	CH_3	83	142—4	63,45	5,60	11,20	$C_{13}H_{14}N_2O_3$	63,39	5,74	11,37
XII	3	H	C_2H_5	75	129—31	64,37	6,34	10,47	$C_{14}H_{16}N_2O_3$	64,59	6,21	10,77
XIII	3	H	C_3H_7	80	109—11	65,50	6,39	10,41	$C_{15}H_{18}N_2O_3$	65,66	6,63	10,21
XIV	3	H	C_4H_9	87	108—9	66,32	6,87	9,53	$C_{16}H_{20}N_2O_3$	66,63	7,00	9,70
XV	3	H	$CH_2CH\text{-}CH_2$	84	140—2	66,20	5,80	10,36	$C_{15}H_{16}N_2O_3$	66,15	5,93	10,28
XVI	3	H	CH_3 $CH(CH_2)_3CH_3$	89	132—4	68,45	7,39	8,74	$C_{18}H_{24}N_2O_3$	68,31	7,66	8,85
XVII	3	H	C_6H_5	87	153—5	69,95	5,17	9,20	$C_{18}H_{16}N_2O_3$	70,11	5,24	9,08
XVIII	3	C_2H_5	C_2H_5	71	69—71	66,39	6,75	9,67	$C_{16}H_{20}N_2O_3$	66,63	7,00	9,70
XIX	3	C_6H_5	C_6H_5	78	160—2	74,90	5,31	7,20	$C_{24}H_{20}N_2O_3$	74,97	5,20	7,37

The phthalimidoacetic and γ-phthalimidobutyric acids were prepared by direct fusion of equimolar amounts of phthalic anhydride and the free amino acid at 145-150°C. The acids were converted to the corresponding acid chlorides on treatment of suspension in dry chloroform with phosphorus pentachloride or thionyl chloride [7, 8]. Amides of the phthalimidocarboxylic acids were prepared by adding equimolar amounts of the corresponding amines to solutions of the acid chlorides in acetonitrile.

The amides of phthalimidocarboxylic acids so obtained are white, crystalline substances which are not soluble in water. Structures of the amides were confirmed by their IR spectra: The stretching vibrations of the carbonyl groups in the phthalimide ring are displayed in the form of two absorption bands in the 1718-1708 and 1765-1735 cm^{-1} regions (according to the literature [9], at 1772-1712 cm^{-1}); and the stretching vibrations of the amide carbonyl, in the 1660-1645 cm^{-1} region. For the monosubstituted amides, an absorption band is observed in the 3320-3225 cm^{-1} region, which is characteristic of NH group stretching vibrations; in the IR spectra of the unsubstituted amides, three absorption bands in the 3415-3210 cm^{-1} region are observed, characteristic of the NH_2 group. The UV spectra of the amides of the ω-(phthalimido)alkyl carboxylic acids (I-XIX) are characterized by the presence of two absorption maxima at 219-220 and 294-296 nm.

EXPERIMENTAL

Pharmacological experiments were performed on mice weighing 18-22 g. The following procedures were used to evaluate substances with anticonvulsant action: The maximum electric shock test (MES) [10]; and the intraperitoneal anticorazole test of [1] (for the most active compounds); toxicity was determined on the intraperitoneal and oral routes of introduction [11]. Results of determining pharmacological action and acute toxicity were treated statistically, calculating ED_{50} and LD_{50} at $P = 0.05$ [12]. On the basis of the data obtained, we calculated the nominal pharmacological width (NPW) — the ratio of ED_{50} to LD_{50}. The data obtained were compared with those for chloracon (Table 2). The compounds were introduced in the form of a suspension in 2% starch mucilage and were considered inactive if they did not exert an anticonvulsant action in doses up to 600 mg/kg. Antibacterial activity of the compounds was determined by the twofold serial dilution method in a liquid growth medium (beef—peptone bouillon). As the test microbes, we used one-day agar cultures of gram-positive *(Staphylococcus aureus)* and gram-negative *(Escherichia coli)* bacteria, which were introduced into a test tube with the bouillon in a dose of 50,000 microbes, with appropriate dilution of the compound being tested. The content of the test tube was incubated in a thermostat for 18-20 h at 37°C, after which the minimum concentration of the substance which stopped growth was determined visually from the intensity or absence of turbidity of the medium in the test tubes. The antibacterial activity of a pharmacopoeia preparation, ethacridine lactate, was determined concurrently.

Of the 20 compounds, ACA was detected in 13 (see Table 2). According to the MES test on intraperitoneal injection, compounds III, VIII, and XX are more active than chloracon; II, XII, and XVIII are approximately equal to it in activity; and I, IV, V, X, XI, XIII, and XIV are less active. Compounds VI, VII, IX, XV, XVI, XVII, and XIX do not have ACA. On oral administration, with respect to MES (and also with respect to the corazole test on intraperitoneal injection), compound III has the same ACA as chloracone; compound XX is approximately 1.5 times as active, and VIII is three times as active. In the intraperitoneal mode of injection, compounds V, VIII, and XVIII are more toxic than chloracon; II, X, XI, XII, XIII, XIV, and XX are approximately equal to it in toxicity; and I, II, and IV are less toxic; on oral administration, all 13 compounds are less toxic than chloracon. The LD_{50} on oral administration is larger than that by intraperitoneal injection by a factor of 2 to 6, and the LD_{50} of the more active compounds (III, VIII, and XX) is greater by a factor of 4 to 6, which indicates their low absorbability into the gastro-intestinal tract; however, the ACA of the compounds develops faster than it does in chloracon; and the NPW is wider than that of chloracon by a factor of 4 to 8. The low toxicity, high ACA, and large NPW make it possible to consider amides of phthalimidoacetic and γ-phthalimidobutyric acids as probable anticonvulsive preparations.

Antimicrobial activity was studied in connection with the known diversity of biological activity of amides containing the phthalimide group in their structure [4-6]; we also determined the effect of the probable anticonvulsant preparations on the microflora of the gastrointestinal system on prolonged use. The amides of the ω-(phthalimido)alkyl carboxylic acids

TABLE 2. ACA and Acute Toxicity of Amides of Phthalimidoacetic and γ-Phthalimidobutyric Acids

Compound	ACA								LD_{50}, mg/kg		LD_{50}/ED_{50}			
	MES				corazole test						MES		corazole test	
	intraperitoneally		internally		intraperitoneally		internally		intraperitoneally	internally	intraperitoneally	internally	intraperitoneally	internally
	action peak, min	ED_{50}, mg/kg	action peak, min	ED_{50}, mg/kg	action peak, min	ED_{50}, mg/kg	action peak, min	ED_{50}, mg/kg						
I	—	285 (228—356)	—	—	—	—	—	—	3100 (2650—3689)	—	10,8	—	—	—
II	30	115 (92—144)	—	—	—	—	—	—	890 (685—1157)	4150 (3217—5354)	7,7	—	—	—
III	30	90 /69—117)	30	213 (176—258)	30	144 (116—179)	30	202 (151—271)	850 (752—961)	4000	9,4	18,0	5,9	19,0
IV	5	200 (152—264)	—	—	—	—	—	—	1550 (1314—1829)	4200 (3333—5292)	7,7	—	—	—
V	10	220 (172—282)	—	—	—	—	—	—	408 (332—502)	1480 (1184—1850)	1,8	—	—	—
VIII	10	50 (44—56)	10	80 (59—108)	10	55 (46—66)	30	66 (51—85)	410 (315—533)	2600 (2301—2938)	8,2	32,5	7,4	39,4
X		200 (154—260)	—	—	—	—	—	—	760 (691—836)	—	3,8	—	—	—
XI	10	152 (116—199)	—	—	—	—	—	—	770 (710—835)	1400 (1102—1778)	5,1	—	—	—
XII	5	133 (102—173)	—	—	—	—	—	—	820 (726—927)	2450 (2042—2940)	6,2	—	—	—
XIII	5	170 (153—188)	—	—	—	—	—	—	760 /679—851)	2230 (1770—2810)	4,5	—	—	—
XIV	5	140 (111—176)	—	—	—	—	—	—	790 (725—861)	2130 (1760—2577)	5,6	—	—	—
XVIII	5	123 (103—146)	—	—	—	—	—	—	420 (331—533)	1600	3,4	—	—	—
XX	10	35 (28—44)	10	155 (117—205)	10	87 (82—92)	30	136 (110—166)	640 (582—704)	2450 (1885—3185)	18,3	15,8	7,3	18,0
Chloracon	15	100 (84—119)	120	230 (209—258)	15	143 (118—179)	120	200 (178—224)	650 (586—722)	1000 (893—1120)	6,5	4,3	4,5	5,0

Note: Limits of fluctuation are given in parentheses.

exerted a slight bacteriostatic action. The minimum bacteriostatic concentration relative to *Staphylococcus aureus* or *Escherichia coli* was 62.5-500.0 μg/ml.

It has been shown previously that unsubstituted acetamide does not have ACA, but the introduction of an aryl substituent into the methyl group leads to its appearance [13]. The data obtained indicate that the introduction of a phthalimido group into the α-position of the acetamide molecule also leads to the appearance of ACA (see Table 2, compound I). Introduction of alkyl substituents into the amide moiety increases ACA (II, III), and the most active of the monosubstituted amides of phthalimidoacetic acid proved to be the ethylamide of phthalimidoacetic acid (III). An increase in the alkyl substituent on the amide nitrogen atom by 1 or 2 methylene groups causes a decrease in ACA (IV, V). Introduction of a second alkyl substituent at the nitrogen atom of the amide group increases the ACA sharply (VIII). The introduction of an unsaturated alkyl radical, aryl radical, or aryl radicals causes a loss of ACA: the allylamide, phenylamide, and diphenylamide of phthalimidoacetic acid have no ACA (VI, VII, IX).

Introduction of a phthalimide group into the γ-position of unsubstituted butyramide, which does not have ACA [13], also leads to the appearance of ACA (X). The laws governing change in ACA on replacement of radicals at the amide nitrogen atom in the γ-phthalimidobutyric acid series are the same as in the phthalimidoacetic acid amide series. For example, the most active proved to be the ethylamide and diethylamide of γ-phthalimidobutyric acid (XII, XVIII). An increase in the alkyl substituent at the amide nitrogen leads to a decrease in ACA (XIII, XIV) or to a complete loss of it, as in the case of γ-phthalimidobutyric acid n-hexylamide (XVI). The allylamide and the amides of γ-phthalimidobutyric acid which have aryl substituents at the amide nitrogen atom, like the corresponding amides of phthalimidoacetic acid, have no ACA (XV, XVII, XIX).

An increase in the number of methylene groups between the phthalimide and amide groups in the molecule from 1 to 3, that is, transition from amides of phthalimidoacetic acid to amides of γ-phthalimidobutyric acid, leads to some reduction in ACA — for example, II is more active than XI; III than XII, VIII than XVIII.

The experimental material accumulated permits one to suggest that the presence of two ethyl groups at the amide nitrogen atom and one methylene group between the amide carbonyl and the phthalimide group is an optimum condition for the manifestation of anticonvulsant action in the series of amides of ω-(phthalimido)alkyl carboxylic acids.

These conditions are satisfied by the diethylamide of phthalimidoacetic acid (VIII) and the morpholide of phthalimidoacetic acid [14], which was previously subjected to biological testing (XX). Both compounds surpass chloracon in ACA.

The IR spectra were taken in vaseline oil on a UR-20 instrument; the UV spectra, in methanol on an SF-16 spectrophotometer.

Amides of ω-(Phthalimido)alkyl Carboxylic Acids. To 0.1 mole of the acid chloride of the ω-(phthalimido)alkyl carboxylic acid in 100 ml of acetonitrile, with stirring, was added 0.1 mole of the appropriate amine in 50 ml of acetonitrile, at room temperature over a 30-minute period. The mixture was kept for 1 h. Then the solvent was evaporated off under vacuum. The residue was crystallized from a 3:1 methanol—water mixture (see Tables 1 and 2).

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SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF AMINOMETHYL DERIVATIVES OF 5- AND 6-HYDROXYBENZOFURAN

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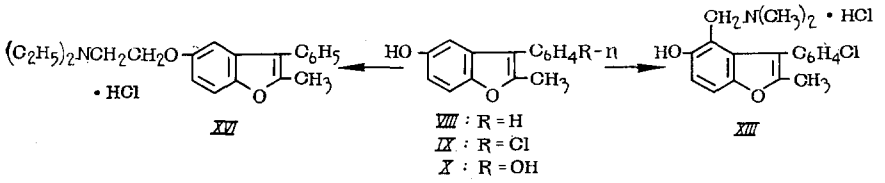
UDC 615.22:547.722].012.1

In view of the interest in benzofuran derivatives as cardiovascular drugs [1, 2] we have synthesized several derivatives of 2-methyl-3-aryl-5- and -6-hydroxybenzofuran and examined some of their pharmacological properties. We used the reaction of substituted α-aryloxypropiophenones (I-III) with polyphosphoric acid by the literature method [3] to prepare several hitherto unknown benzofuran derivatives — 2-methyl-3-(p-chlorophenyl)-5-methoxy- (IV), 2-methyl-3-(p-methoxyphenyl)-5-methoxy- (V), and 2-methyl-3-(p-chlorophenyl)-6-methoxybenzofuran (VI), together with 2-methyl-3-phenyl-5-methoxybenzofuran (VII), which we have described earlier [4].

We synthesized the 5- and 6-hydroxybenzofuran derivatives by demethylating compounds IV-VII with pyridine hydrochloride at 200°C. This gave 2-methyl-3-phenyl-5-hydroxy- (VIII), 2-methyl-3-(p-chlorophenyl)-5-hydroxy- (IX), 2-methyl-3-(p-chlorophenyl)-5-hydroxy- (X), 2-methyl-3-(p-chlorophenyl)-6-hydroxybenzofuran (XI), and 2-methyl-3-phenylbenzofuran (reported earlier [5]).

We examined aminomethylation of the 5- and 6-hydroxybenzofuran derivatives for the synthesis of analogs of the preparation phenykoberan [2]. We found that the 5-hydroxybenzofuran derivatives were aminomethylated at position 4 and the 6-hydroxybenzofurans at position 7; this was supported by the presence in the PMR spectra of the aminomethylbenzofurans of two doublets with J = 9.0 Hz, due to the coupling of the two o-protons.* In this way we synthesized 2-methyl-3-(p-chlorophenyl)-4-dimethylaminomethyl-5-hydroxy- (XIII), 2-methyl-3-phenyl-6-hydroxy-7-dimethylaminomethyl- (XIV), and 2-methyl-3-(p-chlorophenyl)-6-hydroxy-7-dimethylaminomethylbenzofuran (XV).

We also synthesized by the usual method the aminoalkyl ethers of the hydroxybenzofurans, 2-methyl-3-phenyl-5-diethylaminoethoxy- (XVI), 2-methyl-3-phenyl-6-diethylaminoethoxy- (XVII) and 2-methyl-3-(p-chlorophenyl)-6-diethylaminoethoxybenzofuran (XVIII), as the hydrochlorides.



*We have assigned the PMR spectra of 5- and 6-hydroxybenzofuran derivatives earlier [6].

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 0091-150X/80/1402-0104$07.50