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PREPARATION AND BIOLOGICAL ACTIVITY OF THE DERIVATIVES OF PHENYLSUCCINIC ACID. III.* PREPARATION AND ANTICONVULSANT ACTIVITY OF SOME *p*-HALOPHENYLSUCCINIMIDES

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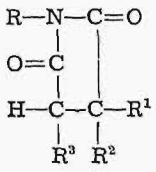
Opisano własności i otrzymywanie imidów i szeregu N-alkiloimidów pochodnych kwasów p-chlorowcofenylobursztynowych. W badaniach czynności przeciwdrgawkowej cztery pochodne, a mianowicie: imid kwasu *p*-fluorofenylobursztynowego oraz imid, N-metyloimid i N-etyloimid kwasu p-bromofenylobursztynowego wykazały bardzo wysoką czynność przeciw drgawkom wywołanym podaniem kardiazolu.

Описаны свойства и получение имидов и ряда N-алкил-имидов производных *n*-галогенфенилянтарной кислоты. В исследованиях противосудорожного действия найдено, что четыре производные, а именно имид *n*-фторфенилянтарной кислоты а также имид, N-метилимид и N-этилимид *n*-бромфенилянтарной кислоты показывают очень сильную активность против судорогам вызванным кардиазолом.

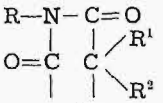
The preparation and properties of *p*-halophenylsuccinimides and some N-alkyl derivatives thereof are described. Four of these compounds namely *p*-fluorophenylsuccinimide, *p*-bromophenylsuccinimide, *N*-methyl- and N-ethyl-p-bromophenylsuccinimides, proved to be potent anticonvulsants againts seizures induced by metrazol.

Although succinimide [1] and some simple N-alkyl derivatives thereof [2] had been synthesized a long time ago, the anticonvulsant activity of the compounds of succinimide structure was disclosed only in the last decade. The comprehensive research by Miller and Long [3–6] who prepared several succinimides of the general formula (A) and tested them for anticonvulsant activity, set forth a novel approach to the basic structural concept (B) which is still regarded as the major determinant of the anticonvulsant activity (barbiturates, hydantoins, oxazolidinediones, acylureas, etc.). Most of these wherein all R = H, alkyls, or phenyl (R^1 is preferably phenyl) compounds showed indeed a more or less distinct anticonvulsant acitvity in mice and rats. This activity was

* Part II, see *Roczniki Chem.*, 36, 1625 (1962).



(A)



(B)

particularly conspicuous in controlling the experimental seizures induced by parenteral administration of metrazol (pentamethylenetetrazol), which are known to respond to drugs similarly as the petit mal seizures in human subjects do. In detailed pharmacological tests [7], two compounds of the series presented by Miller and Long proved to be of therapeutical value. They entered the pharmaceutical markets under the trade names of Milontin (or Phensuximide) (A, wherein R = methyl, R^1 = phenyl, R^2 = R^3 = H) and Celontin (or Methsuximide) (A, wherein R = methyl, R^1 = phenyl, R^2 = methyl, R^3 = H) and are widely used in routine prevention and treatment of petit mal seizures.

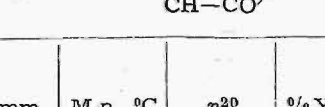
The investigations by Miller and Long involved very many derivatives of phenylsuccinimide, some of them containing various ring substituents. The imide-nitrogen substituents (R) varied from methyl up to butyl and allyl, though the authors suggested that the unsubstituted and N-methyl imides were the most active members of any homologous series.

Since our earlier research [8] made available all four p-halophenylsuccinic acids, we converted them recently to imides and N-substituted imides of the type (A), wherein R^1 = p-halophenyl, R^2 = R^3 = H, and R = H or alkyl. Our aim was to explore the dependence of the anticonvulsant activity on the type of halogen and alkyl substituents. The number of N-homologues prepared and tested for biological activity was considerably increased as compared with the research by Miller and Long, as all straight-chain alkyls and some iso-alkyls were included up to hexyl.

Preparation of p-halophenylsuccinimides followed in general the conventional procedure involving pyrolysis of mono- or diammonium (or amine) salts of the corresponding acids. The salts were prepared by mixing equimolar amounts of the acid and aqueous ammonia or amine, and were processed further without isolation. Higher yields and purer products were noted with hydrogen succinates. The temperature of the reaction mixture during pyrolysis had to be maintained below 175°; otherwise, considerable charring occured which caused difficulty in isolating the products and substantially cut the yield. The imides were purified preferably by recrystallization, though some of the compounds, especially those with the N-substituents of relatively high molecular weight, crystallized extremely slowly. Vacuum distillation was helpful in a few cases of crystallization failure.

Table 1

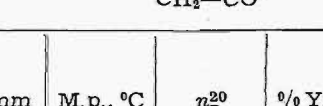
p-Fluorphenylsuccinimides



No	R	Formula	B.p.,°/mm	M.p., °C	n_D^{20}	% Yield	% N		Anticonvulsant activity in		
									metrazol shocks		electr. shocks
							calcd.	found	200 mg/kg	100 mg/kg	200 mg/kg
I	H	$C_{10}H_8NO_2F$	—	128—9	—	63	7.25	7.0	0/5	5/15	4/5
II	CH_3	$C_{11}H_{10}NO_2F$	—	114—16	—	67	6.8	6.85	1/5	6/10	5/5
III	C_2H_5	$C_{12}H_{12}NO_2F$	—	84—6	—	51	6.35	6.7	4/5	—	3/5
IV	C_3H_7	$C_{13}H_{14}NO_2F$	148-52/0.7	—	1.5268	58	5.95	5.65	5/5	—	4/5
V	$CH_2CH{=}CH_2$	$C_{13}H_{12}NO_2F$	155-60/0.2	—	1.5406	62	6.0	5.8	—	—	—
VI	C_4H_9	$C_{14}H_{16}NO_2F$	153-7/0.6	—	1.5222	63	5.6	5.35	4/5	—	5/5
VII	C_5H_{11}	$C_{15}H_{18}NO_2F$	173-7/0.6	21—3	1.5198	48	5.3	5.15	5/5	—	5/5
VIII	*iso*-C_5H_{11}	$C_{15}H_{18}NO_2F$	—	24—7	—	51	5.3	5.1	—	—	—
IX	C_6H_{13}	$C_{16}H_{20}NO_2F$	—	26—8	—	43	5.05	5.15	—	—	—
X	*iso*-C_6H_{13}	$C_{16}H_{20}NO_2F$	—	42—4	—	47	5.05	4.9	—	—	—

Table 2

p-Chlorophenylsuccinimides

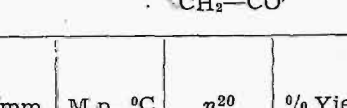


No	R	Formula	B.p., °/mm	M.p., °C	n_D^{20}	% Yield	% N		Anticonvulsant activity in		
									metrazol shocks		electr. shocks
							calcd.	found	200 mg/kg	100 mg/kg	200 mg/kg
XI	H	$C_{10}H_8NO_2Cl$	—	130—2*	—	55*	—	—	—	0/5***	—
XII	CH_3	$C_{11}H_{10}NO_2Cl$	—	107—9*	—	51*	—	—	—	2/5***	—
XIII	C_2H_5	$C_{12}H_{12}NO_2Cl$	—	50—2*	—	38*	—	—	5/5***	—	—
XIV	C_3H_7	$C_{13}H_{14}NO_2Cl$	169-72/0.7	—	1.5529	49	5.55	5.3	—	—	—
XV	$CH_2CH=CH_2$	$C_{13}H_{12}NO_2Cl$	—	61—3*	—	46*	—	—	5/5***	—	—
XVI	C_4H_9	$C_{14}H_{16}NO_2Cl$	240-2/25	25—7	—	58	5.3	5.5	2/5	—	5/5
XVII	C_5H_{11}	$C_{15}H_{18}NO_2Cl$	181-4/2	41—3	—	43	5.0	5.1	—	—	—
XVIII	*iso*-C_5H_{11}	$C_{15}H_{18}NO_2Cl$	—	78—80	—	47	5.0	5.0	—	4/5	4/5
XIX	C_6H_{13}	$C_{16}H_{20}NO_2Cl$	—	19—22	—	53	4.75	4.5	5/5	—	5/5
XX	*iso*-C_6H_{13}	$C_{16}H_{20}NO_2Cl$	—	47—9	—	41	4.75	4.7	—	3/5	3/5

* According to Miller and Long[6].
** 125 mg/dose.
*** 500 mg/dose.

Table 3

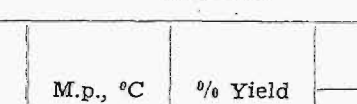
p-Bromophenylsuccinimides



No	R	Formula	B.p., °/mm	M.p., °C	n_D^{20}	% Yield	% N		Anticonvulsant activity in		
									metrazol shocks		electr. shocks
							calcd.	found	200 mg/kg	100 mg/kg	200 mg/kg
XXI	H	$C_{10}H_8NO_2Br$	—	138—9	—	78	5.5	5.6	1/5	5/10	5/5
XXII	CH_3	$C_{11}H_{10}NO_2Br$	—	110—11	—	69	5.2	5.45	0/5	6/15	5/5
XXIII	C_2H_5	$C_{12}H_{12}NO_2Br$	—	69—72	—	62	4.95	5.0	0/5	0/15	3/5
XXIV	C_3H_7	$C_{13}H_{14}NO_2Br$	—	41—3	—	55	4.75	4.8	—	4/5	3/5
XXV	$CH_2CH=CH_2$	$C_{13}H_{12}NO_2Br$	—	69—71	—	55	4.75	4.75	—	4/5	5/5
XXVI	C_4H_9	$C_{14}H_{16}NO_2Br$	194-5/0.6	—	1.5600	56	4.5	4.7	—	4/5	5/5
XXVII	$CH(CH_3)C_2H_5$	$C_{14}H_{16}NO_2Br$	182-3/0.8	54—6	—	58	4.5	4.55	—	4/5	3/5
XXVIII	C_5H_{11}	$C_{15}H_{18}NO_2Br$	—	53—6	—	52	4.3	4.35	—	5/5	5/5
XXIX	*iso*-C_5H_{11}	$C_{15}H_{18}NO_2Br$	—	77—9	—	54	4.3	4.2	—	5/5	5/5
XXX	C_6H_{13}	$C_{16}H_{20}NO_2Br$	—	37—8	—	48	4.15	4.25	—	5/5	4/5
XXXI	*iso*-C_6H_{13}	$C_{16}H_{20}NO_2Br$	—	69—71	—	45	4.15	4.05	—	4/5	5/5

Table 4

p-Iodophenylsuccinimides



No	R	Formula	M.p., °C	% Yield	% N		Anticonvulsant activity in		
							metrazol shocks		electr. shocks
					calcd.	found	200 mg/kg	100 mg/kg	200 mg/kg
XXXII	H	$C_{10}H_8NO_2I$	148—50	83	4.65	4.5	1/5	2/10	5/5
XXXIII	CH_3	$C_{11}H_{10}NO_2I$	105—7	78	4.45	4.25	—	4/5	3/5
XXXIV	C_2H_5	$C_{12}H_{12}NO_2I$	62—3	73	4.25	4.15	—	5/5	3/5
XXXV	C_3H_7	$C_{13}H_{14}NO_2I$	55—7	67	4.1	4.05	—	3/5	5/5
XXXVI	$CH_2CH=CH_2$	$C_{13}H_{12}NO_2I$	77—9	77	4.1	3.95	—	—	—
XXXVII	C_4H_9	$C_{14}H_{16}NO_2I$	54—5	58	3.9	4.05	—	4/5	4/5
XXXVIII	C_5H_{11}	$C_{15}H_{18}NO_2I$	88—90	61	3.75	3.9	—	5/5	4/5
XXXIX	*iso*-C_5H_{11}	$C_{15}H_{18}NO_2I$	54—6	58	3.75	3.95	—	4/5	4/5
XL	C_6H_{13}	$C_{16}H_{20}NO_2I$	55—6	64	3.65	3.55	—	5/5	4/5
XLI	*iso*-C_6H_{13}	$C_{16}H_{20}NO_2I$	74—6	58	3.65	3.45	—	5/5	4/5
XLII	CH_3	$C_{11}H_{11}NO_2I$	71—3	83*	—	—	1/5	9/15	5/10

* According to Miller and Long[3]).

Most of the imides prepared were tested for anticonvulsant activity in the Pharmacological Laboratory, Institute of Drugs, Warsaw. Seven compounds eluded biological testing, owing to very low solubility. The standard testing technique was as follows: the compounds were given orally to mice in a single 200 mg/kg dose, the animals were injected 1 hour later with 100 mg/kg metrazol, and mortality was recorded; the most active compounds were similarly tested in a 100 mg/kg dose. In tests with rats, a 200 mg/kg dose of the compound tested was administered 1 hour before subjecting the animals to electric shoock (0.6 sec., 70 V), and the occurrene of convulsions was recorded. All the compounds were of approximately uniformly acute toxicity of (LD_{50}) 1.5 g/kg.

The physical and analytical data as well as the results of the anticonvulsant screening tests are given in Tables 1—4.

In these tables the effect on the metrazol-induced convulsions is represented as the ratio of the number of lethal cases to the total number of animals tested (for example, ratio 2/5 denotes that the compound was given to 5 mice and in 2 of them it failed to give sufficient protection againts lethal dose of metrazol). The activity in electrically induced convulsions is represented as the ratio of failures to the total number of animals tested (for example, the ratio 3/5 denotes that the compound was given to 5 rats and in 3 cases it failed to prevent convulsions).

The results of biological screening clearly showed that each homologous series might be divided into two subgroups, containing compounds of high activity and of low activity (or even inactive), respectively. The first subgroup contained N-unsubstituted imides and the N-methyl and N-ethyl homologues thereof. The compounds containing five- or six-carbon alkyls proved almost completely inactive; this failure is probably due to some extent to their extremely low solubility in aqueous solutions, which obviously affects resorption.

In series containing various halogen substituents, the three lowest members of the bromine series proved to be most active; an outstanding activity was also observed in the case of *p*-fluorophenylsuccinimide. The activity of these four compounds was evidently higher than that of Milontin, which was used as reference; a detailed pharmacological evaluation is being carried out at present.

The results of biological tests for activity against convulsions induced by an electric shock proved to be of no practical interest.

EXPERIMENTAL

Preparation of *p*-halophenylsuccinimides

p-Fluorophenylsuccinic acid (8 g, 0.0377 mole) was suspended in 15 ml water and 2.5 ml concentrated aqueous ammonia was added. The solution was heated to distil off the water. When the temperature of the reaction mixture reached appro-

ximately 100—110°, the hydrogen ammonium salt began to crystallize out, but melted as soon as the temperature was raised. Pyrolytic decomposition commenced at about 160° as indicated by rapid distillation of water. The melt was maintained at 175° for 2 hours, cooled to approximately 80°, diluted with 20 ml ethanol, treated with charcoal, filtered, and the filtrate left overnight. The crystals collected were recrystallized from 80% ethanol to yield 4.6 g (63%) p-fluorophenylsuccinimide, m.p. 128—9°.

Other imides were prepared similarly. The products which failed to crystallize were purified by vacuum distillation. The pertinent data are tabulated.

Acknowledgements

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OTRZYMYWANIE I AKTYWNOŚĆ BIOLOGICZNA POCHODNYCH KWASU BURSZTYNOWEGO. III. OTRZYMYWANIE I CZYNNOŚĆ PRZECIWDRGAWKOWA IMIDÓW KWASÓW *p*-CHLOROWCOFENYLOBURSZTYNOWYCH

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Kontynuując badania nad zależnością pomiędzy czynnością biologiczną a budową chemiczną pochodnych azotowych kwasów *p*-chlorowcofenylobursztynowych otrzymaliśmy imidy tych kwasów oraz szereg ich N-alkilowych pochodnych. Związki te otrzymaliśmy stosując konwencjonalną metodę pirolizy odpowiednich soli amonowych lub aminowych. Najlepsze rezultaty osiągnęliśmy poddając pirolizie sole kwaśne. Otrzymane pochodne, stanowiące analogi strukturalne leków przeciwdrgawkowych Milontin i Celontin (Miller i Long[3–6]), badano pod względem czynności przeciwdrgawkowej. W badaniach na myszach 3 najniższe człony każdej serii, tj. imid niepodstawiony oraz pochodne N-metylowa i N-etylowa, wykazały bardzo wysoką zdolność hamowania drgawek wywołanych przez injekcyjne podanie kardiazolu. Pochodne z wyższymi podstawnikami alkilowymi (od propylowego do heksylowego) wykazały bardzo niską czynność lub były nieczynne. Wszystkie badane związki wykazały brak zdolności hamowania drgawek wywołanych u szczurów przez szok elektryczny. Cztery spośród otrzymanych związków (I, XXI, XXII i XXIII) wykazały czynność wyższą niż Milontin i są obecnie przedmiotem szczegółowych badań farmakologicznych.