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ANTICONVULSANTS. N-BENZYLAMIDES

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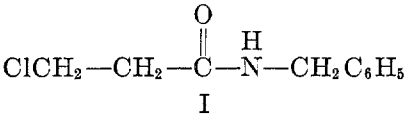
In the course of investigation of compounds prepared in this laboratory, it was noted that several compounds which contained a benzylamide residue had pronounced anticonvulsant activity when tested either audiogenically or by means of the electroshock test in rats. This observation led to the preparation of 40 compounds including N-benzyl-β-chloropropionamide (I) or "Hibicon", a product having a 4+ rating in both audiogenic and electroshock tests. This compound has been found on extensive clinical trial (1) to be effective in the treatment of grand mal.



I

The simple aliphatic derivatives as represented by compounds 1 through 8 in Table I show an apparent decrease of activity in the audiogenic rating and a rapid drop in electroshock activity as the aliphatic side chain is increased.

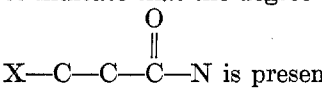
Compounds 9 through 12 in the table involve the replacement of the hydrogen in the side chain by an aromatic grouping. In general, activity drops to zero with the exception of N-benzylphenoxyacetamide (No. 10), which maintained a moderate audiogenic activity at high dosage.

Compounds 13 through 20 represent the interchange, for comparative study, of the sulfonamido group for the carbonylamido residue. As in the previously discussed aliphatic series, activity decreases with increasing side chain, the most active compounds being Nos. 18 and 20—the N-benzylamides of ethane- and benzene-sulfonic acids.

In general, the preparation of the dibasic amides and those of aromatic acids resulted in compounds lacking in activity. On the other hand halogenation had a pronounced positive effect in increasing the rating. The substitution of chlorine for hydrogen led to more active compounds than substitution by bromine or iodine. The compounds thus synthesized were also less toxic than the parent.

Polychlorination as in compounds 28, 29 shows no additive effect in rating over that of the monosubstituted compound No. 26.

The tremendous increase in activity of the β-substituted propionamides seems to indicate that the degree of activity should be at a maximum when the system



is present, for halogenation on carbons other than of the β-carbon results in a marked decrease of activity in the electroshock test. In this group, No. 32 (N-benzyl-β-chloropropionamide) seems to be the drug of choice,

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TABLE I

PROPERTIES OF N-BENZYLAMIDES

NO.	PRODUCT	M.P., °C.	FORMULA	ANALYSIS						ACTIVITY* mg./Kilo body weight	
				Calc'd			Found				
				C	H	N	C	H	N	Audiogenic	Electroshock
1	N-Benzyl propionamide	52–53 42–43 A 42.6–43.7 B	$C_{10}H_{13}NO$			8.6			8.4	++ 100 ip.	+ 100 ip.
2	N-Benzyl-*n*-butyramide	41–44 36–38 A 39–39.8 B	$C_{11}H_{15}NO$			7.3			7.6	+ 50 ip.	– 50 ip.
3	N-Benzyl isocaproamide	26–27.5 <35 A	$C_{13}H_{19}NO$	76.1	9.3	6.8	75.6	9.4	6.9	– 300 ip.	– 300 ip.
4	N-Benzyl heptoamide	52–53.5	$C_{14}H_{21}NO$			6.4			6.3	+++ 400 ip.	– 400 ip.
5	N-Benzyl pelargonamide	66–69	$C_{16}H_{25}NO$	77.7	10.1	5.7	77.3	10.4	5.6	++ 360 ip.	– 400 ip.
6	N-Benzyl lauramide	89–91.5 82–83 A	$C_{19}H_{31}NO$			4.5			4.5	– 500 ip.	– 500 ip.
7	N-Benzyl myristamide	89–90 89–90 A	$C_{21}H_{35}NO$			4.4			4.7	– 250 ip.	– 500 ip.
8	N-Benzyl palmitamide	92–93 94.5–95 A	$C_{23}H_{39}NO$	76.5	10.8	3.9	76.5	10.9	4.2	– 500 ip.	– 500 ip.
9	N-Benzyl cinnamamide	94–96.5	$C_{16}H_{15}NO$	81.0	6.3	5.9	80.6	6.5	5.4	– 400 ip.	– 400 ip.

10	N-Benzyl phenoxyacetamide	85–86 84.5–86 A	$C_{15}H_{15}NO_2$	74.7	6.2	5.8	74.8	6.6	5.8	+++ 400 ip.	− 400 ip.
11	N-Benzyl-α-phenoxypropionamide	87.5–88.5	$C_{16}H_{17}NO_2$			5.5			5.7	− 500 ip.	− 500 ip.
12	N-Benzyl-β-phenylpropionamide	84.5–86.5 84–85 A	$C_{16}H_{17}NO$	80.3	7.1	5.9	80.6	7.5	6.1	− 500 ip.	− 500 ip.
13	N-Benzyl-p-xylenesulfonamide	75–78	$C_{15}H_{17}NOS$	65.5	6.2	5.1	65.5	6.6	5.2	− 400 ip.	− 400 ip.
14	N-Benzyl-p-nitrobenzenesulfonamide	124–126	$C_{13}H_{12}N_2O_5S$			9.6			10.0	+ 500 ip.	− 500 ip.
15	N-Benzyl-m-nitrobenzenesulfonamide	95–98	$C_{13}H_{12}N_2O_5S$			9.6			9.7	− 500 ip.	− 500 ip.
16	N,N′-Dibenzyl-m-sulfobenzodiamide	127.5–129	$C_{21}H_{18}N_2O_3S$			7.6			7.0	− 500 ip.	− 500 ip.
17	N-Benzylphenylmethanesulfonamide	144–146	$C_{14}H_{15}NO_2S$			5.3			5.3	− 250 ip.	− 500 ip.
18	N-Benzylethanesulfonamide	56–58	$C_9H_{13}NO_2S$			7.0			7.1	+ 100 ip.	± 100 ip.
19	N-Benzyl-β-naphthalenesulfonamide	118.5–122	$C_{17}H_{15}NO_2S$			4.7			4.9	− 500 ip.	− 500 ip.
20	N-Benzylbenzenesulfonamide	85–86	$C_{13}H_{13}NO_2S$			5.7			5.7	+ 100 ip.	± 100 ip.
21	N,N′-Dibenzylfumaramide	290 dec. 203.5–205 A	$C_{18}H_{18}N_2O_2$	73.5	6.1	9.5	73.3	6.5	10.0	− 500 ip.	− 500 ip.

TABLE 1—*Concluded*

NO.	PRODUCT	M.P., °C.	FORMULA	ANALYSIS						ACTIVITY* mg./Kilo body weight	
				Calc'd			Found				
				C	H	N	C	H	N	Audiogenic	Electroshock
22	N,N′-Dibenzyladipamide	189–190.5 188–189 A	$C_{20}H_{24}N_2O_2$			8.6			8.4	– 500 ip.	– 500 ip.
23	N,N′-Dibenzylsuccinamide	213.5–216 205–206A	$C_{18}H_{20}N_2O_2$			9.5			9.1	– 500 ip.	– 500 ip.
24	N,N′-Dibenzylphthalamide	179–181.5 178–179 A	$C_{22}H_{20}N_2O_2$			8.1			8.2	– 500 ip.	– 500 ip.
25	N-Benzyl-β-naphthamide	140–143	$C_{18}H_{15}NO$			5.4			5.7	– 500 ip.	– 500 ip.
26	N-Benzylchloroacetamide	91–92 93–93.6 B	$C_9H_{10}ClNO$			7.6			7.4	++ 150 ip.	– 150 ip.
27	N-Benzylbromoacetamide	106–107.5	$C_9H_{10}BrNO$			6.1			6.2	– 50 ip.	– 50 ip.
28	N-Benzyldichloroacetamide	94–95.5 94.8–95.6 B 90.3 D	$C_9H_9Cl_2NO$			6.4			6.3	+ 100 ip.	– 100 ip.
29	N-Benzyltrichloroacetamide	93.5–94.2 93.6–94.4 B 90–91 E	$C_9H_8Cl_3NO$			5.6			5.5	+ 100 ip.	– 100 ip.
30	N-Benzyl-α-chloropropion-amide	80–82	$C_{10}H_{12}ClNO$	60.8	6.1	7.1	61.2	6.2	7.0	– 125 ip.	

31	N-Benzyl-α-bromopropionamide	93.5–94.5	$C_{10}H_{12}BrNO$			5.8			6.0	++ 200 ip.	− 200 ip.
32	N-Benzyl-β-chloropropionamide	94	$C_{10}H_{12}ClNO$	60.8	6.1	7.1	60.8	6.3	7.1	++++ 125 ip.	++++ 125 ip.
33	N-Benzyl-β-bromopropionamide	102–103 F	$C_{10}H_{12}BrNO$	49.6	5.0	5.8	49.4	5.3	5.9	++++ 250 ip.	+++ 325 ip.
34	N-Benzyl-β-iodopropionamide	117–118 F	$C_{10}H_{12}INO$	41.5	4.2	4.8	41.4	4.6	5.1	++ 300 ip.	− 200 ip.
35	N-Benzyl-γ-chlorobutyramide	70–72 F 68 C	$C_{11}H_{14}ClNO$	62.4	6.6	6.6	62.6	6.7	7.0	++++ 125 ip.	± 125 ip.
36	N-(p-Chlorobenzyl)-β-chloropropionamide	125–126 F	$C_{10}H_{10}Cl_2NO$	51.0	5.1	6.1	51.5	5.2	6.1	++++ 175 ip.	± 175 ip.
37	N-Propyl-β-chloropropionamide	54–56	$C_6H_{12}ClNO$	48.2	8.1	9.5	48.8	8.4	9.4	++ 350 ip.	± 325 ip.
38	N,N-Diphenyl-N-benzylurea	104–106	$C_{20}H_{18}N_2O$			9.3			9.5	− 500 ip.	− 500 ip.
39	Hexyl N-benzyl carbamate	liquid at r. t.	$C_{14}H_{21}NO$			6.0			5.8	+++ 100 ip.	± 100 ip.
40	Chloroethyl N-benzylcarbamate	42–44.5	$C_{10}H_{12}ClNO_2$			7.1			6.7	++++ 100 ip.	± 100 ip.

* Significance of ratings. The compounds are tested at the highest dose which does not produce visible symptoms of drug action. The maximal theoretical protection is 4+. A Prepared previously from the corresponding ester by O. C. Dermer and Jack King (3). B Prepared previously from the ester by Buchler and MacKenzie (4). C Prepared by W. F. Hanford and Rodger Adams (5). D Prepared by McKie (6). E Prepared by Braun, Jostes, and Munch (7). F No. 33–36 recrystallized from ether-petroleum ether.

showing a very high (4+) rating in both the audiogenic and electroshock test with very low toxicity. If No. 32 is *para*-chlorinated as in No. 36, the electroshock rating is partially destroyed. The replacement of the N-benzyl group of the highly active No. 32 with an *n*-propyl group (No. 37) shows a specific decrease.

The replacement of the regular acid groups by the carbonic and carbamic acids as represented by compounds 38, 39, and 40 shows moderate activity for this substitution.

The complete results of the pharmacological tests are reported elsewhere (2).

In general, the desired benzylamide was synthesized by the direct reaction of the corresponding acid chloride with two moles of benzylamine in ice, or by the simultaneous addition of 1 mole of alkali and amine at 0–5°. The preparation of N-benzylphenylmethanesulfonamide required temperatures upward from 50° to get a satisfactory yield.

It should be noted that the m.p. of the N-benzylcinnamamide prepared by us was more than 100° lower than that reported by Dermer and King (3) who prepared their amide by aminolysis. This may be due to *cis-trans* isomerism.

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EXPERIMENTAL

N-Benzyl-α-chloropropionamide. (Method A) To 40.3 ml. of benzylamine in 150 cc. of water at −5° was added, dropwise and simultaneously with vigorous stirring, 48 grams of α-chloropropionyl chloride and 14.8 g. of sodium hydroxide in 50 cc. of water. After allowing the reaction mixture to come to room temperature, the desired product was filtered and washed with ice-water. Yield 35.5 gms., m.p. 74–76°; after two recrystallizations from ether and petroleum ether it melted at 80–82°.

N-Benzylpelargonamide. (Method B) To 30 gms. of benzylamine (0.28 mole) rapidly stirred in crushed ice was added dropwise 24.7 (0.14 mole) of pelargonyl chloride. The reaction mixture was filtered and washed with water. This solid, after recrystallization from methanol, melted at 66–69°; yield 29 g.

SUMMARY

The preparation of 23 new benzylamides is reported; these compounds were tested for anticonvulsant activity. One of them has been found to be active clinically in the treatment of grand mal.

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