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SYNTHESIS OF BENZAMIDES, AND THEIR ANTISPASMODIC AND ANTIHYPOXIC PROPERTIES*

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Benzamides are known as physiologically active substances, and individual members of this series of compounds have found application as anticonvulsants, e.g., metaclopramid (4-amino-5-chloro-N′-(2-diethylaminoethyl)-2-methoxybenzamide hydrochloride) [2], procainamide [4-amino-N-(2-diethylaminoethyl)benzamide] [3] and its structural analogues [4, 5], which display pronounced antispasmodic activity. N-Aryltrimethoxybenzamides [6, 7] and N-aryltrifluoromethylbenzamides [8] are among the other compounds of this series known to exhibit antispasmodic properties. In general, research into the antispasmodic properties of N-substituted benzamides has been more comprehensive than for the N-unsubstituted compounds, although a number of isolated reports have appeared on the antispasmodic effects of the latter class.

In order to make a more detailed study of the antispasmodic properties of N-unsubstituted benzamides, to assess the effect of the benzene ring substituents on these properties and to provide a more complete picture of their pharmacological activity, we synthesized 15 compounds in this series and determined their toxicity, and antispasmodic and antihypoxic activity.

A convenient way of synthesizing N-substituted benzamides is by using urea. Several aromatic hydrocarbons have been directly amidated in the presence of Lewis acids [9] to produce 10-20% yields, while N-unsubstituted benzamides have been obtained in high yield by heating the appropriate acids with urea in oleum [10]. However, the low yields achieved using the former method and the over-aggressive medium of the latter limits their broad application as a preparative technique. We have developed a modified approach to synthesizing N-unsubstituted benzamides with urea. Benzamides I-XV were obtained in moderate yields (up to 58%) by reacting the corresponding acids with urea in formic acid. We have used this system in previous investigations as an effective amidating and azacyclizing reagent in a number of chemical reactions, e.g. for synthesizing benzhydrylformamides [11]. The R and R′ substituents have virtually no effect on the reaction rate or the product yields.

$$RR'C_6H_3CONH_2$$

I—XV

R=H, R′=H(I), p-F(II), *o*-F(III), *o*-Cl(IV), *m*-Cl(V), p-Cl(VI), *o*-I(VII), *m*-I(VIII), p-I(IX), *m*-NO_2(X), p-NO_2(XI), *m*-MeO(XII), p-MeO(XIII), p-Me(XIV); R=*o*-Cl, R′=*m*-Cl(XV).

The yields and physicochemical characteristics of the benzamides I-XV that were synthesized using this method are shown in Table 1, while the method itself is described below in the "Experimental (Chemical)" section.

Antispasmodic activity of compounds I-XV was assessed using the conventional screening tests, namely maximum electric shock (MES) and Corazol titration; numerical results are given in Table 2. The antihypoxic properties of the benzamides were determined using models of acute hemic, histotoxic, and hypoxic hypoxia with hypercapnia (Table 3).

It was found from the investigation of toxicity (see Table 2) that all the benzamides studied (I-XV) were low-toxic substances (LD_{50} > 1000 mg/kg).

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TABLE 1. Yields and Physicochemical Properties of Benzamides I-XV

Compound	Yield, %	mp, °C	Empirical Formula	IR Spectrum, ν_{max}, cm^{-1}	
				C=O	NH_2
I	43	131—2	C_7H_7NO	1679	3415, 3440
II	41	152—3	C_7H_6FNO	1690	3353, 3390
III	40	115—7	C_7H_6FNO	1682	3420, 3460
IV	48	140—1	C_7H_6ClNO	1670	3408, 3430
V	51	130—1	C_7H_6ClNO	1675	3394, 3425
VI	49	178—80	C_7H_6ClNO	1679	3407, 3435
VII	53	181—2	C_7H_6INO	1674	3414, 3445
VIII	56	183—5	C_7H_6INO	1680	3400, 3430
IX	48	215—7	C_7H_6INO	1675	3400, 3435
X	50	143—4	$C_7H_6N_2O_3$	1723	3467, 3480
XI	58	199—200	$C_7H_6N_2O_3$	1692	3438, 3470
XII	45	125—7	$C_8H_9NO_2$	1685	3450, 3475
XIII	39	164—6	$C_8H_9NO_2$	1662	3418, 3440
XIV	46	155—6	C_8H_9NO	1690	3450, 3475
XV	57	205—6	$C_7H_5Cl_2NO$	1673	3465, 3495

TABLE 2. Toxicity, Breadth of Therapeutic Effect (BTE), and Antispasmodic Activity of Benzamides I-XV

Compound	Dose, mg/kg	MES			Corazol Convulsion Threshold, mg/kg		LD_{50}, mg/kg	BTE[2]
		% of prevented convulsions	% survival of animals	ED_{50}, mg/kg	$M \pm m$	ACI[1]		
I	200	16,7	100	100	120,4±9,3	1,13	1000	7,7
	100	50,0	100		(p 0,195)			
II	200	50,0	100	200	150,9±15,1	1,42	1000	5,0
	300	83,3	83,3		(p 0,015)			
III	200	100	100	27	116,6±2,8	1,17	1110	41,1
	50	83,3	100		(p 0,002)			
	25	50,0	100					
IV	200	100	100	100	158,8±22,0	1,35	1000	10,0
	150	66,7	100		(p 0,002)			
	100	50,0	100					
V	200	83,3	83,3	100	286,8±67,2	2,50	1000	10,0
	100	66,7	100		(p 0,031)			
VI	200	50,0	83,3	200	106,8±10,4	0,91	1210	6,1
	250	66,7	83,3		(p 0,442)			
VII	200	100	100	50	324,5±15,3	3,31	1000	20,0
	100	83,3	100		(p 0,000)			
	75	66,7	100					
VIII	200	16,7	50,0	244	148,4±5,1	1,26	1000	4,1
	300	83,3	100		(p 0,005)			
IX	200	66,7	100	170	113,7±14,0	1,04	1000	5,9
	150	33,3	100		(p 0,770)			
X	200	50,0	100	180	106,7±19,9	0,98	1000	5,6
	150	33,3	83,3		(p 0,922)			
XI	200	33,3	100	224	100,0±5,1	0,94	1000	4,5
	300	66,7	100		(p 0,341)			
XII	200	16,7	100	288	133,9±7,2	1,16	1000	3,5
	300	50,0	100		(p 0,081)			
XIII	200	16,7	66,7	—	88,2±12,1	0,83	1000	—
					(p 0,192)			
XIV	200	33,3	100	286	120,4±6,6	1,10	1000	3,5
	300	50,0	100		(p 0,223)			
XV	200	100	100	77	196,3±30,5	1,80	1000	12,9
	100	66,7	100		(p 0,021)			
	50	50,0	100					

Note. [1]Anti-corazol index; [2]breadth of therapeutic effect.

It can be seen from the findings of the experiments (Table 2) that almost all the compounds investigated possess antispasmodic activity when measured by the MES test, the only exception being para-methoxybenzamide XIII. In this test the ortho halogen-substituted benzamides III and VII, whose ED_{50} values were similar to those typical of the classic anticonvulsants, displayed higher antispasmodic activity than the unsubstituted benzamide I. Introduction of substituents into the para and meta positions of benzamide reduced antispasmodic properties in compounds II, VI, and VIII-XIV. It is interesting that the effect of the substituents in the para position of the benzamide is independent of the radical type, i.e., its electron-donor or electron-acceptor properties. In a similar way the nature of the substituents in the meta position have no influence on the antispasmodic activity (as measured by the MES test) of compounds VIII, X, and XII relative to benzamide I; the exceptions here are the meta-chlorobenzamide derivatives V and XV, which demonstrated significant anticonvulsant activity.

TABLE 3. Antihypoxic Activity of Benzamides I-XV

Compound	Sodium nitrite, 300 mg/kg			Sodium nitroprusside, 25 mg/kg			Pressurized chamber		
	control	test	AHI	control	test	AHI	control	test	AHI
I	33,6±1,6	25,0±2,1 0,008	0,70	15,2±3,7	14,8±1,6 0,922	0,97	28,0±0,4	25,8±0,8 0,043	0,90
II	33,6±1,6	27,2±2,5 0,090	0,80	15,2±3,7	15,7±2,99 0,922	1,00	28,0±0,4	28,5±0,9 0,400	1,00
III	16,3±0,8	15,7±1,9 0,770	0,96	12,6±0,9	19,5±3,4 0,062	1,59	24,0±0,8	29,8±2,9 0,102	1,23
IV	33,6±1,6	40,7±5,8 0,261	1,20	11,7±1,4	11,5±1,9 0,922	0,98	31,6±1,8	50,5±2,2 0,000	1,60
V	33,6±1,6	28,5±2,96 0,168	0,80	15,2±3,7	14,7±2,4 0,922	0,97	28,0±0,4	34,7±2,2 0,047	1,20
VI	33,6±1,6	20,7±1,1 0,005	0,60	15,2±3,7	12,5±1,5 0,500	0,80	28,0±0,4	28,0±1,3 1,000	1,00
VII	27,8±2,2	32,7±2,7 0,297	1,20	11,7±1,4	13,0±0,17 0,563	1,10	31,6±1,8	44,2±3,3 0,007	1,40
VIII	27,8±2,2	27,3±2,9 0,922	0,98	11,7±1,40	9,0±0,7 0,123	0,80	31,6±1,8	23,8±2,9 0,562	1,10
IX	27,8±2,2	26,3±1,3 0,562	0,95	13,8±1,9	13,2±0,3 0,770	0,96	31,6±1,8	37,3±2,6 0,102	1,20
X	33,6±1,6	26,7±4,50 0,195	0,80	11,7±1,40	13,2±2,6 0,629	1,10	28,0±0,4	26,2±1,4 0,400	0,90
XI	33,6±1,6	25,0±2,6 0,080	0,70	11,7±1,4	10,5±0,9 0,500	0,90	28,0±0,4	26,6±1,5 0,400	0,90
XII	27,8±2,2	24,2±1,8 0,226	0,87	13,8±1,9	16,3±1,6 0,341	1,20	31,6±1,8	39,3±2,3 0,019	1,24
XIII	33,6±1,6	20,7±0,9 0,004	0,60	11,7±1,4	9,7±1,3 0,297	1,10	28,0±0,4	29,8±1,7 0,347	1,10
XIV	20,0±0,6	24,8±1,9 0,037	1,24	11,3±0,6	10,2±0,5 0,192	0,90	37,0±1,8	37,2±1,9 0,347	1,00
XV	27,8±2,2	24,5±0,9 0,192	0,88	13,8±1,2	13,8±2,2 1,000	1,00	31,6±1,6	38,6±4,3 0,165	1,20

Note. Preparations were investigated in 1/10 LD_{50} dosage (see Table 2). AHI stands for antihypoxic index.

Antispasmodic properties measured in terms of Corazol titration were almost entirely absent among the para-substituted benzamides (II, VI, IX, XI, XIII and XIV). However, considerable antispasmodic activity was exhibited by ortho-iodobenzamide VII and meta-chloro benzamide derivatives V and XV, which also displayed pronounced antispasmodic effects in the MES test. It was seen from an overall comparative analysis of the findings from the 2 tests (see Table 2) that the greatest antispasmodic activity is displayed by halogensubstituted benzamides, the halogen atom being located preferably in the ortho or meta positions of the benzamide. It is interesting that in the benzhydrylurea series, another class of compounds exhibiting antispasmodic effects, derivatives with ortho and meta-halide substituents in the benzene ring also prove to be the most active [12].

It is worth noting that the introduction of 2 chlorine atoms into the benzene ring (compound XV) increased the activity relative to benzamide I and its mono-substituted derivatives IV and VI, although the effects of the substituents were nonadditive.

From an investigation of antihypoxic properties it was found that benzamides I-XV were either inactive or slightly active with regard to the development of acute hemic and histotoxic hypoxia induced by sodium nitrite (300 mg/kg) and sodium nitroprusside (25 mg/kg) respectively (see Table 3). Thus, for example, only compound XIV displayed moderate antihypoxic activity on the hemic hypoxia model and only ortho-fluorobenzamide III on the histotoxic hypoxia model. Benzamides I-XV, particularly ortho-benzamide IV, proved more effective when investigated using the model of hypoxic hypoxia with hypercapnia (see Table 3).

In summary, it was found that there are in the N-substituted benzamide series several promising compounds which afford highly active anticonvulsants after a number of functional changes. On the whole the benzamides investigated displayed low activity as regards the alleviation of hypoxic states.

EXPERIMENTAL (CHEMICAL)

IR spectra of the synthesized compounds were recorded on a UR-20 spectrophotometer (Germany) in a Vaseline oil suspension.

A 0.05 mole sample of benzoic acid and 0.2 moles of urea in 25 ml of formic acid were heated on a metallic bath to 130°C and kept at this temperature for 1 h. Then the temperature was raised to 180°C over the following 1 h. Reaction com-

pletion was determined by means of TLC on Silufol UV-254 plates (8:2 benzene–ethanol eluting system, UV light detection). On completion the reason mixture was poured into 200 ml of cold water and the unreacted benzoic and formic acids were neutralized with alkali. The precipitate was filtered off and recrystallized from water to yield 2.6 g (43%) of benzamide I. Benzamides II-XV were synthesized and isolated in a similar way to compound I.

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