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INVESTIGATION OF THE ANTICONVULSANT AND ANTIHYPOXIC ACTIVITY OF NEW DIBENZAZEPINE DERIVATIVES

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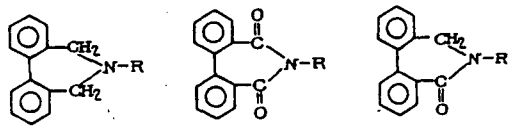
Derivatives of dibenzazepine (finlepsin, imipramine) and benzdiazepine (sibazon, nozepam, chlordiazepoxide, etc.) are used widely in medical practice as psychotropic preparations [4].

Results are given in the present study of a search for new biologically active compounds among derivatives of dibenzazepine, which possess anticonvulsant and antihypoxic activity. The combination of these forms of activity is of particular interest in the treatment of epilepsy, when the hemodynamics and metabolism of the brain are disturbed and an epileptic fit is accompanied by asphyxia.

Derivatives of the following dibenzazepines have been synthesized and investigated: 6,7-dihydro-5H-dibenz[c,e]-azepine (I), 6,7-dihydro-5H-dibenz[c,e]azepine-5,7-dione (II), and 6,7-dihydro-5H-dibenz[c,e]azepin-7-one (III).



I, IV a-d *II, V* a-c *III, VI* a-p

R=H (I—III); CHO (IVa); Ac (IVb, Va, VIa), F_3Ac (IVc, Vb, VIg), EtCO (VIb), PrCO (VIc), *i*-PrCO (VId), BuCO (VId), *i*-BuCO (VIf), PhCO (IVd, Vc, VIh), o, m, p-ClC_6H_4CO (VIi-h), o, m-FC_6H_4CO (VIl, n), m-MeC_6H_4CO (VIn), m-$MeOC_6H_4CO$ (VIo), p-$NO_2C_6H_4CO$ (VIp).

The initial dibenzazepines (I)-(III) for acylation have been described previously [3, 6, 7]. The data of elemental analysis, IR spectra, and melting points of compounds (I)-(III) obtained correspond to those given in the literature. The procedures for synthesis are given in the chemical experimental section and differ significantly from those described in [1].

The acylation of (I)-(III) with acetic and trifluoroacetic anhydrides and with the acid chlorides of aliphatic (C_3-C_5) carboxylic and benzoic acids is described below.

The acylation of the NH group in (I)-(III) was confirmed by the IR spectra of the compounds obtained. The absorption of the secondary NH group, observed in the starting materials at 3200-3300 cm^{-1}, was absent as was an intense absorption in the 1050-1300 cm^{-1} region, the ester band, which rules out the possibility of O-acylation.

EXPERIMENTAL (CHEMICAL)

The IR spectra of the compounds synthesized were taken on an IR 21 spectrometer (Nujol mulls). A check on the course of reactions and the purity of the compounds obtained was effected using Silufol UV-254 plates in the system benzene–ethanol (9:1). Visualization was with UV light. The characteristics of the compounds obtained are given in Table 1. The data of elemental analysis corresponded to calculated values.

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TABLE 1. Dibenzazepine Derivatives Synthesized

Compound	mp, °C	Empirical formula
IVa	176—8	$C_{15}H_{13}NO$
IVb	94—6	$C_{16}H_{15}NO$
IVc	91—3	$C_{16}H_{12}FNO$
IVd	138—40	$C_{21}H_{17}NO$
Va	212—5	$C_{16}H_{11}NO_3$
Vb	215—7	$C_{16}H_8FNO_3$
Vc	194—6	$C_{21}H_{13}NO_3$
VIa	120—2	$C_{16}H_{13}NO_2$
VIb	104—5	$C_{17}H_{15}NO_2$
VIc	92—3	$C_{18}H_{17}NO_2$
VId	79—81	i-$C_{18}H_{17}NO_2$
VIe	69—70	$C_{19}H_{19}NO_2$
VIf	71—2	i-$C_{19}H_{19}NO_2$
VIg	186—8	$C_{16}H_{10}FNO_2$
VIh	156—7	$C_{21}H_{15}NO_2$
VIi	121—2	$C_{21}H_{14}ClNO_2$
VIj	133—5	$C_{21}H_{14}ClNO_2$
VIk	181—2	$C_{21}H_{14}ClNO_2$
VIℓ	134—5	$C_{21}H_{14}FNO_2$
VIm	154—5	$C_{21}H_{14}FNO_2$
VIn	110—2	$C_{22}H_{17}NO_2$
VIIo	108—9	$C_{22}H_{17}NO_3$
VIp	208—9	$C_{21}H_{14}NO_4$

Preparation of 6,7-Dihydro-5H-dibenzic[c,e]azepine (I). A mixture of diphenic aldehyde (10.5 g; 0.05 mole), formamide (6.9 ml; 0.17 mole), and formic acid (3.75 ml; 0.1 mole) was heated for 2 h at 160°C. The formal derivative obtained was isolated from the reaction mixture by adding water (50 ml). The precipitated solid was filtered off and dried. Compound (IIIa) (10.6 g; 95%) was obtained. The formyl derivative was then hydrolyzed with conc. HCl (10 ml) in ethanol (30 ml) by boiling for 1 h and then cooling to 5-10°C. Compound (I) hydrochloride (9.4 g; 80%) was precipitated, mp 280-282°C. Treatment of (I) hydrochloride with saturated aqueous sodium carbonate solution gave compound (I) base (7.1 g; 70%), mp 104-105°C [7].

Preparation of 6,7-Dihydro-5H-dibenzic[c,e]azepine-5,7-dione (II). A mixture of diphenic acid anhydride (5.6 g) and conc. ammonia (60 ml) was heated at 100°C for 1 h by which time the solid anhydride had dissolved completely. Dilute HCl was poured into the cooled reaction mixture until a weakly acidic reaction was given. The precipitated solid was filtered off and recrystallized from ethanol. Compound (II) (4.5 g) of mp 178-180°C was obtained [3].

Preparation of 6,7-Dihydro-5H-dibenzic[c,e]azepine-7-one (III). A mixture of 2-formyldiphenyl-2-carboxylic acid (22.6 g; 0.1 mole), formic acid (22.2 ml; 0.6 mole), and urea (48 g; 0.8 mole) in ethyleneglycol (50 ml) was heated at 180°C for 1 h. The reaction mixture was then diluted with water (50 ml), the solid filtered off, and recrystallized from ethanol. Compound (III) (16.9 g) of mp 194-196°C was obtained [6].

Acetylation of Compounds (I)-(III). Compound (I), (II), or (III) (0.05 mole) was heated with Ac_2O (30 ml) at 90-95°C for 2 h. The end of the reaction was determined by TLC after which the mixture was diluted with water (100 ml). The precipitated solid was filtered off and purified by recrystallization from ethanol. The yields of acetyl derivatives (IVb), (Va), and (VIa) were 75-80%.

Acylation with C_3-C_5 Aliphatic Acid Chlorides. A mixture of compound (III) (0.05 mole), benzene (50 ml), and the appropriate C_3-C_5 aliphatic acid chloride (0.055 mole) was heated at the boiling point for 2-4 h. The end of the reaction was detected by TLC. The benzene was then distilled off, the residue was treated with aqueous sodium bicarbonate solution to neutral reaction, the solid filtered off, and recrystallized from aqueous ethanol. The yield of acyl derivatives (IVb-f) was 65-80%.

Trifluoroacetylation of (I)-(III). Compound (I), (II), or (III) (0.05 mole) was mixed with benzene (50 ml) and $(CF_3CO)_2O$ (0.55 mole) was added with vigorous stirring during 1 h from a dropping funnel. The stirring was continued for 1-2 h further until complete disappearance of (I), (II), or (III) (analysis by TLC).

Benzylation of (I)-(III). Compound (I), (II), or (III) (0.05 mole) was heated in a mixture of pyridine (20 ml) and benzoyl chloride (or with a substituted benzol chloride) (0.055 mole) at 120°C for 3-8 h. The end of the benzoylation reaction was also determined by TLC [disappearance of the spot for the initial azepine (I), (II), or (III)]. The reaction mixture was then diluted with 15% HCl to convert the pyridine into its water-soluble hydrochloride salt and the benzoyl derivative of (I), (II), or (III) was precipitated. The solid was filtered off and recrystallized from aqueous ethanol. The yield of the benzoyl derivative of (I), (II), or (III) was 60-70%.

TABLE 2. Acute Toxicity, Anticonvulsant Activity, and Breath of Therapeutic Action of Dibenzazepine Derivatives

Compound	LD_{50}, mg/kg	Breadth of therapeutic action	Dose, mg/kg	MES			Convulsion threshold of Corazol, mg/kg		
				% convulsions prevented	% animals surviving	ED_{50}, mg/kg	$M \pm m$	p	ACO
VIa	—	—	200	60,0	100	170	111,3±23,9	0,560	1,11
			150	50,0	50,0				
VIb	>2000	9,1	200	50,0	66,7	220	86,4±15,3	0,165	0,79
			250	66,7	100				
VIc	>1000	3,8	200	16,7	50,0	264	117,8±10,6	0,444	1,08
			300	50,0	100				
VId	>2000	7,6	200	16,7	33,3	264	108,5±14,0	0,922	1,00
			300	50,0	100				
Va	>2000	13,4	200	66,7	100	149	125,2±8,7	0,073	1,20
			100	33,3	100				
Vb	1980	9,0	200	50,0	100	220	110,0±7,5	0,922	1,01
			250	66,7	100				
VIa	—	—	200	50,0	83,3	225	146,2±21,3	0,016	1,42
			300	83,3	100				
VIb	—	—	200	50,0	100	180	127,9±20,7	0,297	1,24
			150	33,0	66,7				
VIc	—	—	200	33,3	33,3	274	226,7±55,1	0,050	2,16
			300	50,0	66,7				
VId	—	—	300	33,3	33,3	520	346,6±18,1	0,000	3,12
			500	50,0	83,3				
VIe	—	—	500	66,7	100	390	255,5±36,9	0,003	2,44
			300	33,3	50,0				
VIf	—	—	200	16,7	66,7	550	119,9±9,5	0,400	1,08
			300	33,6	16,7				
			600	50,0	66,7				
VIg	900	40,9	90	100	100	22	128,0±9,7	0,062	1,20
			30	66,7	100				
			15	33,3	83,3				
VIh	>2000	9,5	200	40,0	60,0	210	108,2±6,2	0,300	1,08
			250	83,3	100				
VIi	>2000	13,9	200	66,7	83,3	144	106,9±8,8	0,500	1,10
			100	33,3	100				
VIj	2420	13,4	200	66,7	100	180	106,7±5,0	1,000	1,10
			150	33,3	100				
VIk	>2000	30,8	200	83,3	83,3	65	143,3±6,9	0,000	1,40
			100	66,7	83,3				
			50	50,0	66,7				
VIℓ	>2500	8,7	200	33,3	66,7	287	90,0±3,8	0,120	0,90
			300	50,0	83,3				
VIm	>2500	24,5	200	100	100	102	101,9±1,4	0,698	1,02
			100	50,0	83,3				
			150	83,3	100				
VIn	>2500	15,0	200	66,7	100	167	101,2±4,4	0,845	1,02
			150	40,0	100				
VIo	>2000	42,6	200	100	100	47	117,6±13,2	0,223	1,20
			100	100	100				
			50	50,0	100				
			25	33,3	66,7				
VIp	>2000	12,0	200	60,0	100	166	79,3±13,7	0,165	0,80
			150	33,3	50,0				

EXPERIMENTAL (PHARMACOLOGICAL)

The acute daily toxicity, anticonvulsant, and antihypoxic activity of the compounds under investigation were determined in random-bred mice (18-25 g) on intragastric administration.

Assessment of the anticonvulsant activity was carried out by the generally accepted screening tests, viz. maximal electroshock (MES) [9] and Corazol 'titration' [8]. The anticonvulsant action of preparations was judged by their ability to take away the tonic-extensor component of convulsions, and to prevent the death of animals observed in controls under the action of MES, and by the increse in the threshold of convulsions caused by an intravenous infusion of Corazol. A comparative assessment of the anticonvulsant activity was carried out using values of the Ed_{50} found by the method of Litchfield and Wilcoxon [2] for MES and the anticorazole index (ACI) for corazol titration.

The antihypoxic properties of the compounds studied were made apparent in three models of the acute hypoxic state, viz. Hemic hypoxia caused by intraperitoneal administration of sodium nitrite (300 mg/kg), histotoxic hypoxia caused by intraperitoneal administration of sodium nitroprusside (25 mg/kg), and hypoxic hypoxia with hypercapnia (animals were placed

TABLE 3. Antihypoxic Activity of Dibenzazepine Derivatives

Compound	Dose, mg/kg	Sodium nitrite, 300 mg/kg			Sodium nitroprusside, 25 mg/kg			Sealed chamber		
		control	expt.	AHI	control	expt.	AHI	control	expt.	AHI
VIb	200	41,5±2,9	40,6±5,1 0,929	0,98	11,3±0,6	13,8±0,5 0,011	1,22	—	—	—
VIc	100	20,0±0,6	28,5±2,6 0,006	1,43	11,3±0,6	12,0±0,6 0,442	1,06	—	—	—
VId	200	32,2±3,7	31,0±2,1 0,442	0,91	11,3±0,6	10,0±0,6 0,628	0,88	33,0±2,2	33,2±1,4 0,923	1,01
Va	200	25,2±2,2	21,0±0,9 0,102	0,83	13,5±0,7	13,6±2,5 1,000	1,01	30,6±1,7	28,8±2,7 0,562	0,94
Vb	200	—	—	—	11,3±0,6	11,0±0,9 0,770	0,97	—	—	—
Vc	200	—	—	—	11,3±0,6	11,6±0,6 0,698	1,03	—	—	—
VIg	30	18,2±0,9	16,8±1,0 0,297	0,92	—	—	—	—	—	—
	90	18,2±0,9	32,5±2,5 0,001	1,79	13,8±1,2	18,6±0,95 0,007	1,35	29,0±1,9	44,3±2,6 0,001	1,53
VIh	200	13,0±1,1	24,2±2,0 0,001	1,86	10,0±1,1	11,5±0,8 0,297	1,15	30,2±2,1	33,8±1,7 0,223	1,12
VIi	200	13,0±1,1	21,0±0,9 0,000	1,62	10,0±1,1	10,7±1,4 0,698	1,07	30,2±2,1	38,3±3,9 0,102	1,27
VIj	200	13,0±1,1	17,7±0,2 0,003	1,36	10,0±1,1	9,7±1,3 0,845	0,97	30,2±2,1	33,2±1,1 0,223	1,10
VIk	200	13,0±1,1	13,8±0,7 0,562	1,06	10,0±1,1	10,3±1,1 0,442	1,03	23,0±0,7	26,3±1,3 0,037	1,14
VIℓ	200	13,0±1,1	17,5±0,8 0,009	1,35	10,0±1,1	10,5±1,1 0,770	1,05	30,2±2,1	35,8±2,5 0,120	1,19
VIm	200	13,0±1,1	16,2±1,0 0,062	1,25	10,0±1,1	12,8±0,3 0,052	1,28	30,2±2,1	38,5±1,8 0,013	1,27
VIn	200	13,0±1,1	20,5±2,1 0,008	1,58	9,0±1,1	12,5±0,6 0,022	1,39	30,2±2,1	28,3±0,6 0,389	0,94
VIo	200	20,0±0,9	22,5±2,5 0,389	1,13	9,0±1,1	10,2±1,0 0,442	1,13	30,2±2,1	32,2±2,6 0,562	1,07
VIp	200	16,3±0,8	16,8±0,7 0,628	1,03	12,3±0,9	11,8±0,9 0,698	0,96	24,3±0,8	23,5±0,9 0,500	0,97
Sodium hydroxybutyrate	350	18,3±0,4	23,0±1,9 0,031	1,26	13,5±0,9	13,8±0,8 0,845	1,02	45,2±2,1	58,3±1,2 0,000	1,29

in a sealed chamber of 250 ml capacity) [5]. The effectiveness of preparations was assessed by their antihypoxic index (AHI), the ability to prolong the survival of animals of the experimental groups compared to control groups.

All the preparations investigated were introduced as suspensions in 1% starch paste, 1.5 h before introducing the convulsant or hypoxant.

The experimental data obtained were processed statistically and are given in Tables 2 and 3.

The compounds investigated had low toxicity, the LD_{50} varied from 900 to 2500 mg/kg and more. The breath of the therapeutic action (LD_{50}/Ed_{50} for MES) was in the range from 2.8 to 42.6 (see Table 2, columns 2, 3).

As is evident from Table 2 the anticonvulsant activity according to the MES test was more marked for the dibenzasepinone derivatives (VIg, k, o), for which the values of ED_{50} were 22, 65, and 47 mg/kg respectively. The greatest percentage prevention of the tonic phase of convulsions on MES was also recorded for mice receiving this group of preparations at a dose of 1/5-1/10 LD_{50} (VIg, k,o). The percentage prevention of convulsions for the remaining acyl derivatives of dibenzazepinones varied from 33.3 to 66.7 (see Table 2).

The anticonvulsant effect of dibenzazepines and dibenzasepinediones was weak [16.7-33.3%; (IVd), (Va)] to moderate [50.0-66.7%; (IVa, b), (Va, b)]. The high percentage survival of animals receiving all the compounds investigated should be noted. This indicator has a dose-dependent character. On increasing the dose the percentage survival of animals undergoing MES increased.

A significant increase in the convulsion threshold of Corazol was also displayed more frequently by the action of dibenzazepinones than by the action of dibenzazepines and dibenzazepinediones. The ACI of the active compounds varied from 1.40 to 3.12. Acylation of compounds at the amino group by C_3-C_5 aliphatic acid chlorides leads to a sharp reduction in the anticonvulsant activity in the MES test, with the exception of the trifluoroacetylated derivative (VIg). Compounds (VIa, c-e) display more marked anti-convulsant action on Corazol convulsions, which is characteristic of tranquilizers and neuroleptics with a sedative component. The introduction of a benzoyl radical into all the groups of compounds did not confer anticonvulsant properties onto them, although their toxicity was sharply reduced, particularly for the benzoylated derivative of dibenzazepinone. However the use of a residue with chlorine in the para position (VIk) and a hydroxymethyl group in the meta

position (VIo) of the benzene ring increased significantly the anticonvulsant activity in the MES test and for compounds (VIk-i) in the Corazol test (see Table 2).

The presence of marked anticonvulsant action in preparations (VIg, k, o) makes the search for this kind of pharmacological activity among acyl derivatives of dibenzazepinone attractive.

The antihypoxic activity of the compounds investigated was also marked for the dibenzazepinones. The dibenzazepinediones displayed little antihypoxic activity but among the dibenzazepines compound (IVb) was active in the histotoxic hypoxia model and compound (IVc) against hemic hypoxia. A high antihypoxic effect was seen against all the models among the dibenzazepinone (VIg). Its antihypoxic activity exceeded that of sodium hydroxybutyrate, the standard preparation (Table 3). Almost all the benzene derivatives of dibenzazepinone displayed high antihypoxic activity in the hemic hypoxia model [see Table 3, (VIh-j, l, n)]. In the histotoxic hypoxia model only compounds (VIk, m) significantly prolonged the survival of animals (see Table 3).

The investigations carried out showed that the most promising compound for in-depth study as an anticonvulsant agent with antihypoxic properties was the trifluoro-acetylated derivative of dibenzazepinone (VIg).

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