3,5-DIMETHYL-5-p-ALKOXYPHENYLHYDANTOINS AND THEIR NEUROTROPIC PROPERTIES

I. A. Dzhagatspanyan, L. V. Azaryan,
G. G. Melikyan, I. M. Nazaryan,
S. A. Avetisyan, O. L. Mndzhoyan, and
K. A. Tatevosyan

UDC 615.214.32:547.783].03.07

Serious forms of epilepsy and social adaptation of patients have recently been treated with anticonvulsant drugs which also possess antiparaoxysmal, anxiolytic, and antiamnesic activity. Of particular interest are hydantoins showing both anticonvulsant properties and the ability to restore memory loss [7].

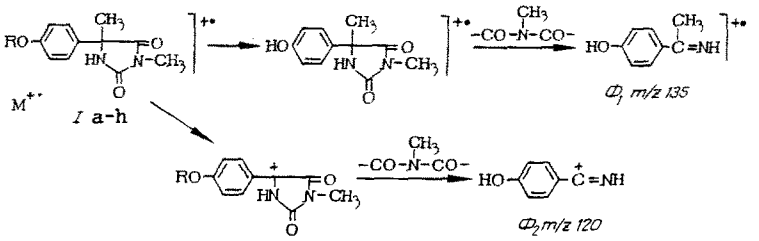
In order to obtain novel anticonvulsant drugs with atypical activity, eight alkyoxphenylmethylhydantoins have been synthesized, and their neurotropic activity examined (Ia-h).

Introduction of a methyl group into the 3-position of the hydantoin ring is known to increase anticonvulsant activity and reduce toxicity [9].

The simpler alkyl groups are usually introduced using haloalkanes or dimethyl sulfate [5]. We have used methyl iodide to methylate 5-methyl-5-p-alkoxyphenylhydantoins [1].

EXPERIMENTAL (CHEMISTRY)

TLC was carried out on bound layers of KSK silica gel–gypsum using benzene–ethyl acetate–acetic acid (7:3:1) as the mobile phase, and phosphomolybdic acid (5% alcoholic solution) as developer, temperature of development 60-70°C. Mass spectra were obtained on a MX-1320 mass spectrometer with direct introduction of the sample into the ion source, ionizing electron energy 70 eV. The molecular ion peaks corresponded to the molecular masses of the compounds. The formation in the mass spectra of fragments Φ_1 and Φ_2 by elimination of the $-CON(CH_3)CO-$ grouping proves the position of the introduced methyl group. Table 1 shows the mass numbers and cleavage of the molecular ions, and the intensities of fragments Φ_1 and Φ_2, for these compounds.



R=CH_3 (a), C_2H_5 (b), C_3H_7 (c), iso C_3H_7 (d), C_4H_9 (e), iso-C_4H_9 (f), C_5H_{11} (g), isoC_5H_{11} (h)

3,5-Dimethyl-5-p-alkoxyphenylhydantoins (Ia-h). To 0.02 mole of the 5-methyl-5-p-alkoxyphenylhydantoin (I) in 100 ml of 25% sodium carbonate solution was added 2.84 g (0.02 mole) of methyl iodide. The mixture was heated at 40-50°C for 6 h, and the resulting crystalline solid filtered off and recrystallized from 50% ethanol (Table 1).

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 25, No. 3, pp. 32-34, March, 1991. Original article submitted April 20, 1990.

TABLE 1. 3,5-Dimethyl-5-p-alkoxyphenylhydantoins (Ia-h)

Compound	Yield, %	mp, °C	R_f	Empirical formula	M^+	Φ_1	Φ_2
Ia	90,5	112—3	0,72	$C_{12}H_{14}N_2O_3$	—	—	—
Ib	86,7	118—9	0,75	$C_{13}H_{16}N_2O_3$	248(54)	6	30
Ic	90,8	149	0,70	$C_{14}H_{18}N_2O_3$	262(58)	14	32
Id	85,4	183—4	0,71	$C_{14}H_{18}N_2O_3$	262(30)	14	24
Ie	92,0	125—6	0,72	$C_{15}H_{20}N_2O_3$	276(84)	16	32
If	84,6	165—6	0,73	$C_{15}H_{20}N_2O_3$	276(38)	12	16
Ig	81,2	147	0,75	$C_{16}H_{22}N_2O_3$	290(50)	14	22
Ih	80,0	116	0,70	$C_{16}H_{22}N_2O_3$	290(50)	14	20

Note. The elemental analyses were in satisfactory agreement with the calculated values.

TABLE 2. Comparative Anticonvulsant Activities of 3,5-Dimethyl-5-p-alkoxyphenylhydantoins (Ia-h)

Compound	Antagonism to corazole, ED_{50}, mg/kg	$[PI]_{cor}$	Electric shock, ED_{50}, mg/kg	$[PI]_{el}$	Disturbance of motor coordination, TD_{50}, mg/kg	$[TI]_{cor}$	Acute toxicity, LD_{50}, mg/kg	$[TI]_{el}$
Ia	105(45,6+241,5)	2,3	170(109,6+263,5)	1,4	250(122,0±512,0)	18,0	1900(633,3+570,0)	11,2
Ib	140(63,6+308)	1,2	165(133,0—204,6)	1,06	175(109,3—280,0)	8,0	1115(930,0—1337,0)	6,7
Ic	250(161,2—387,5)	1,1	175(110,0—278,2)	1,7	295(100,2—796,5)	8,6	2400(2000—2904)	13,7
Id	58(29—116)	9,6	175(110,0—278,2)	3,2	560(400—806,4)	42,2	2450(1960—3062,5)	14,0
Ie	54(24,5—28,8)	3,3	185(146,8—233,1)	0,9	180(102,8—315,0)	35,1	1900(633,3—5700)	10,5
If	87(54,3—139,2)	4,02	320(170—608)	1,01	350(212,1—577,5)	12,8	1115(945—1315,7)	3,4
Ig	95(55,8—161,5)	2,8	185(155,4—220,1)	1,4	270(195,6—372,6)	18,4	1750(1000—3062,5)	9,5
Ih	87(54,3—139,2)	6,4	155(110,7—217)	3,4	560(400—806,4)	20,6	1800(1161,3—2790)	11,6
Mesantoin	7,2(3,6—15,4)	10,5	18	4,2	76(69,6—82,9)	41,6	300	16,6
Diphenine	—	—	21(16,7—26,5)	2,7	56,4(49,7—64,0)	—	190(181,3—199,1)	9,05

Notes. $[PI] = TD_{50}/ED_{50}$ is the protective index for corazole; $[PI]_{el} = TD_{50}/LD_{50}$ for electric shock; $[TI]_{cor} = LD_{50}/ED_{50}$, therapeutic index for corazole; $[TI] = LD_{50}/ED_{50}$ for electric shock. Confidence levels given in brackets for $P = 0.05$.

EXPERIMENTAL (PHARMACOLOGY)

The pharmacological exmination of the 5-p-alkoxyphenyl-3,5-dimethylhydantoins was carried out in comparison with the well known antiepileptic drugs diphenine (5,5-diphenylhydantoin), mesantoin (5-ethyl-3-methyl-5-phenylhydantoin), the anxiolytic seduxen (diazepam), and the nootropic piracetam (nootropil) [3, 7, 10, 11]. The drugs wre administered during the day, intraperitoneally, 45 minutes before the commencement of the test, as suspensions in Tween-80. The effects of the compounds at each dose level were examined in 6-10 animals per group. The control animals received the emulsifier.

The criterion for anticonvulsant activity was the prevention in mice of clonic convulsions induced by administration of corazole, elimination of tonic extension in the maximum electric shock test [1], and antagonism to nicotine hypertension and arecoline tremor [2].

The anxiolytic (tranquillizing) activity of the most active comopund (Id) was assessed in comparison with diphenine and mesantoin using the conflict situation method [8]. Conflict was aroused in rats by the confrontation of two motivations, namely feeding and defensive.

The antiamnesic activity of (Id) and the reference drugs in rats was assessed by the passive flight conditioned reflex (PFCR) followed by the application of an electric shock as the amnesic factor using the method of Bures and Buresova [4] in a modified form.

The neurotoxicity of all the comopunds (disturbance of motor coordination, myorelaxation and ataxis in mice) was determined by the rotating rod method. Also found was the acute daily toxicity in mice, and the 50% effective (ED_{50}) and lethal (LD_{50}) doses established. The results of the tests for anxiolytic and antiamnesic activity were evaluated statistically [1, 2].

At doses as low as 54-105 mg/kg (ED_{50}), these hydantoins showed strong antagonism to corazole, and in doses of 155-320 mg/kg they prevented tonic electrical convulsions in mice. Increasing the anticonvulsant dose several times resulted in myorelaxation, ataxis, and disturbance of motor coordination. Further increases in the dose resulted in the deaths of the

TABLE 3. Anxiolytic and Antiamnesic Activity of Compound Id Compared to Mesantoin, Diphenine, Diuzepam, and Piracetam

Compound (dose, mg/kg)	Anxiolytic effect			Antiamnesic effect			
				time, s			
				light chamber		dark chamber	
				day of experiment			
	No. of punishments on taking water	No. of approaches to drink	No. of movements	1	2	1	2
Emulsifier	3,5(2,0 — 4,96)	3,0(1,2 — 4,8)	36,3(22 — 50,6)	14,1(9,2 — 19,1)	5,0(2,9 — 7,0)	165,9(160,9 — 170,8)	175,0(172,9 — 177,0)
Id (25)	14(7,3 — 20,7)	7,4(5,4 — 9,4)	56,9(13,4 — 100,4)	5,0(2,9 — 7,0)	130,8(50,1 — 211,5)	175,0(172,0 — 177)	—*
Mesantoin (10)	31,4(10 — 52,8)	5,0(2,7 — 4,7)	216,7(159 — 279,4)	9,3(4,0 — 146)	160(111 — 209)	170,6(165,3 — 181,2)	—*
Diphenine (40)	14,2(3,6 — 24,8)	12,6(1,1 — 24,1)	198,8(73,0 — 390,3)	5,4(2,6 — 8,2)	151,6(82,2 — 221)	174,6(171,8 — 177,4)	—
Diphenine (60)	6,0(2,8 — 2,2)	2,4(1,7 — 3,1)	25,2(18,3 — 32,9)	—	—	—	—
Diazepam (2)	16,0(7,7 — 24,3)	14,1(7,5 — 21,7)	160,6(72,2 — 249)	—	—	—	—
Piracetam (100)				33,6(22,7 — 44,5)	133,2(86,2 — 180,2)	146,9(136,4 — 157,4)	—*

Note. In parentheses: confidence interval for p = 0.05. Asterisks: statistical treatment was not done because the results were of zero significance in the majority of cases.

animals. The most active compound was (Id) R = iso-C_3H_7). The spectrum of action of this compound showed it to possess anticonvulsant activity against corazole and electrical shock, at doses far removed from the neurotoxic and toxic levels. The protectant and therapeutic indices for corazole were 9.6 and 42.2 respectively, but none of the compounds affected nicotine hyperkinesis or arecoline tremor. These methylhydantoins were reminiscent in their effects of mesantoin and diphenine, although unlike these dephenine is virtually devoid of anticorazole activity, and shows high neurotoxicity (Table 2).

In conflict situations in rats, at doses as low as 25 mg/kg compound (Id), like the tranquillizer diazepam, increased by a factor of four the basic parameters, viz., punishable taking of water, showing that this compound has anxiolytic activity. Under the same conditions, mesantoin (10 mg/kg) also increased the number of occasions when water was taken (by a factor of nine). There was a marked increase in motor activity. In doses of 40 mg/kg and 60 mg/kh, diphenine did not cause any increase in the basic index of anxiolytic activity (Table 3).

In model electric shock amnesia (PFCR), compound (Id) in a dose of 25 mg/kg, like the well known nootrope piracetam, extended the repetition time of the reflex in rats. After 24 h, the animals receiving (Id) remained in the light chamber for 130.8 sec, which is some 26 times longer than this time for the control animals (5 sec) receiving emulsifier. This indicates the presence of antiamnesic activity in these compounds. Administration of diphenine (40 mg/kg) and mesantoin (10 mg/kg) also resulted in an increase in the residence time in the light chamber, by factors of 30.3 and 32 respectively (Table 3).

These 3,5-dimethyl-5-p-alkoxyphenylhydantoins thus include compounds of low toxicity which possess anticorazole and antielectric shock activity. The most active compound is (Id), which like the analogous methylhydantoin mesantoin also shows anxiolytic and antiamnesic types of activity. However, diphenine, which does not contain a methyl radical, while showing antiamnesic activity, is almost devoid of anticorazole and tranquillizing properties.

Current view of the mode of action of diphenine show it to affect the GABA (benzodiazepine—receptor complex) [6]. The different effects of the methylated and unmethylated hydantoins could therefore be due to stronger ligand-receptor interactions with the benzodiazepine receptors of the methyl compounds, and stereochemical factors could also play a part.

The combination of anticonvulsant, anxiolytic, and antiamnesic activity which these studies have revealed in methylated hydantoins encourages further synthesis of compounds of this type.

LITERATURE CITED

1. L. V. Azaryan, S. A. Avetisyan, N. E. Akopyan, et al., Khim.-farm. Zh., No. 8, 55-58 (1978).
2. L. V. Azaryan, O. L. Mndzhoyan, S. A. Avetisyan, et al., ibid., No. 7, 808-813 (1983).
3. M. D. Mashkovskii, Recent Advances in Neuropharmacology [in Russian], Leningrad (1982), pp. 107-111.
4. J. Bures and O. Buresova, J. Comp. Physiol. Psychol., 56, 286-272 (1963).
5. K. H. Dudly and D. L. Bius, J. Org. Chem., 34, No. 4, 1133-1136 (1969).
6. D. W. Gallager, P. Mallorga, and J. F. Tallman, Brain Res., 189, 209-220 (1980).
7. C. Guizgea, H. Mouravie, and F. Lesuisse, Neuro-psychopharmacology, Oxford (1978), pp. 1623-1631.
8. W. Haefel, L. Pieri, and R. Schafner, General Pharmacology and Neuropharmacology of Benzodiazepine Derivatives, Berlin (1981), p. 262.
9. Martindale, The Extra Pharmacopeia, 28th Edn., London (1985), p. 1251.
10. J. V. Millichap, Physiological Pharmacology, 2B, 97-143 (1965).
11. W. P. Tsun-Hon and T. Sau-Fun, Jpn. J. Pharmacol., 49, No. 3, 309-315 (1989).