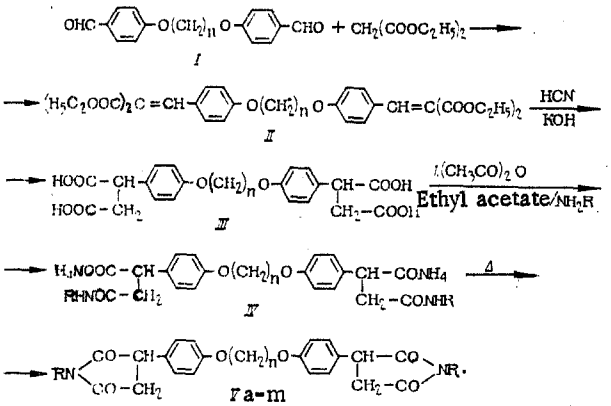
RELATIONSHIP BETWEEN CHEMICAL STRUCTURE AND ANTICONVULSIVE ACTIVITY IN 4,4'-(α,ω-ALKYLENEDIOXY)DIPHENYLSUCCINIMIDES

N. S. Nesunts, S. A. Avetisyan,
I. A. Dzhagatspanyan, N. E. Akopyan,
and O. L. Mndzhoyan

UDC 615.213.015.1.07

The relationship between chemical structure and anticonvulsant activity has recently been studied [1, 2] in some new succinimide derivatives. Since the structure of the receptors [3] which interact with anticonvulsant drugs, in particular pufemid, is as yet unknown, it was of interest from a chemical-biological point of view to determine the distances between the active centers in these receptors by simultaneously blocking them with a single molecule containing two succinimide residues. For this purpose, we have synthesized some 4,4'-(α,ω-alkylenedioxy)diphenylsuccinimides (Va-m) as follows:



Va: $n = 1$; Vb: $n = 2$; Vc: $n = 3$; Vd, f: $n = 4$; Ve: $n = 4$ [$-CH(CH_3)(CH_2)_2$]; Vg: $n = 5$; Vh, i $n = 6$; Vj: $n = 7$; Vk: $n = 8$; Vl: $n = 9$; Vm: $n = 10$; Va-e, g, h, j-m: R = H; Vf: R = CH_3; Vi: R = Na.

The bis-(4-formylphenoxy)alkanes (I) were obtained by alkylation of p-hydroxybenzaldehyde with the appropriate dihaloalkanes (Table 1), or by the Vilsmeier method [4-6]. We attempted the synthesis of these compounds by the formylation of α,ω-diphenoxyalkanes [7], but the yields of aldehydes were no better than 30%.

In the alkylation of p-hydroxybenzaldehyde with dihaloalkanes in a ratio of 2:1, the reaction did not proceed to completion, with the result that, in addition to (I), α,ω-haloalkoxybenzaldehydes (Table 2) were formed, but as the length of the alkyl chain increased, so did the yield of the main product (I).

TABLE 1. Bis-(4-formylphenoxy)alkanes (I)

n	Yield, %	mp, °C	Found, % C	Found, % H	Molecular formula	Calculated, % C	Calculated, % H	R_f (A)
1	50,3	84—5 [6]	70,00	5,02	$C_{15}H_{12}O_4$	69,53	5,02	0,20
2	55,3	117—8 [4]	71,58	5,44	$C_{16}H_{14}O_4$	71,11	5,18	0,20
3	63,2	135—6 [4]	74,90	5,90	$C_{17}H_{16}O_4$	75,35	5,63	0,35
4	66,3	135—40 [4]	72,09	5,90	$C_{18}H_{18}O_4$	72,49	6,04	0,37
4 [$-CH(CH_3)(CH_2)_2$]	68,0	60—1	72,20	6,55	$C_{18}H_{18}O_4$	72,48	6,04	0,43
5	72,0	94—5 [6]	72,97	6,41	$C_{19}H_{20}O_4$	73,00	6,41	0,52
6	73,5	98—101	73,44	6,50	$C_{20}H_{22}O_4$	73,61	6,71	0,55
7	75,0	63—4	74,42	7,20	$C_{21}H_{24}O_4$	74,12	7,00	0,61
8	76,5	81—2	74,77	7,51	$C_{22}H_{26}O_4$	74,57	7,34	0,64
9	77,2	82—3	74,74	7,57	$C_{23}H_{28}O_4$	75,00	7,60	0,67
10	78,5	75—6	75,20	8,00	$C_{24}H_{30}O_4$	75,39	7,85	0,69

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 7, pp. 801-806, July, 1983. Original article submitted July 29, 1982.

 0091-150X/83/1707-0480$07.50

TABLE 2. α,ω-Dihaloalkoxybenzaldehydes

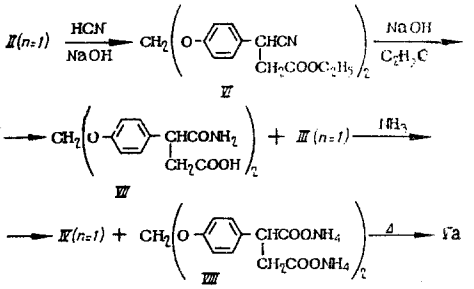
n	Hal	Yield, %	mp or bp, °C	Found, % C	Found, % H	Found, % Hal	Molecular formula	Calculated, % C	Calculated, % H	Calculated, % Hal	R_f (A)
3	Br	15	145–150*	47,03	3,79	35,02	$C_9H_9O_2Br$	47,19	3,93	34,88	0,78
3	Cl	12	145–150 (5 mm Hg) [4]	60,40	5,43	17,63	$C_{10}H_{11}O_2Cl$	60,49	5,54	17,90	0,56
4	Br	6	149–153 (5 mm Hg)	58,80	5,90	35,62	$C_{11}H_{13}O_2Br$	58,67	5,78	35,56	0,48

*From 50% alcohol.

The dialdehydes (I) were converted by the Knoevenagel reaction [8] into the corresponding bismalonates (II), which are new compounds with the exception of (II, n = 4), which has been described in a patent [9] (Table 3).

Addition of hydrogen cyanide to the double bond in the malonates (II) followed by hydrolysis of the addition product in glycol [10] afforded the disuccinic acids (III) which were then converted into (Va-m) as shown.

In the case of (II, n = 1), the addition of hydrogen cyanide was hindered by the formation of by-products [1], and the reaction was therefore carried out in such a way as to obtain the nitriloester (VI) [11], which on subsequent hydrolysis gave a mixture of the disuccinamic and disuccinic acids. On heating with ammonia, this mixture afforded the disuccinimide (Va).



The structures of the compounds obtained were confirmed by UR spectroscopy and mass spectrometry, and purity was checked by TLC and elemental analyses.

EXPERIMENTAL CHEMISTRY

TLC was carried out on bound layers of KSK silica gel-gypsum with mobile phases: ether–light petroleum, 3:2 (A), developer iodine vapor, and phenol–xylene–formic acid, 3:7:2 (B), developer bromophenol blue. IR spectra were obtained on a UR-20 spectrometer (East Germany), and mass spectra on an MX 1320 instrument.

α,ω-Bis-(4-formylphenoxy)alkanes (I) [4]. To the alkoxide obtained from 23.81 g (1.04 mole) of metallic sodium and 600 ml of absolute alcohol was added 122.05 g (1.0 mole) of p-hydroxybenzaldehyde, and the mixture was boiled for 4 h. The dihaloalkane (0.5 mole) was then added, and heating continued for 48 h. The resulting (I) was filtered off and recrystallized from 50% ethanol (Table 1). To the filtrate after removal of the ethanol under reduced pressure was added 200 ml of water, the mixture extracted with ether, the ether extracts dried over sodium, and after removal of the solvent the residue was redistilled or crystallized

TABLE 3. Tetraethyl α,ω-Alkylenebis(hydrophenylmalonates) (II)

n	Yield, %	mp or bp, °C (mm Hg)	Found, % C	Found, % H	Molecular formula	Calculated, % C	Calculated, % H	R_f (A)
1	80,5	52–3	64,58	6,01	$C_{29}H_{32}O_{10}$	64,44	5,93	0,25
2	81,5	122–5	65,09	6,59	$C_{30}H_{34}O_{10}$	64,74	6,47	0,25
3	82,3	63–4	63,30	6,10	$C_{31}H_{36}O_{10}$	63,73	6,34	0,33
4	83,1	98–100 [9]	71,22	6,34	$C_{32}H_{38}O_{10}$	71,56	6,42	0,35
4 (–CH(CH$_3$)(CH$_2$)$_2$)	84,5	220–40 (1)	66,12	6,47	$C_{32}H_{38}O_{10}$	65,98	6,53	0,36
5	85,2	76–7	66,12	6,77	$C_{33}H_{40}O_{10}$	66,44	6,71	0,38
6	86,7	115–7	67,49	6,95	$C_{34}H_{42}O_{10}$	67,10	6,57	0,45
7	87,3	121–2	67,61	7,32	$C_{35}H_{44}O_{10}$	67,30	7,05	0,49
8	88,0	106–7	67,50	7,50	$C_{36}H_{46}O_{10}$	67,71	7,21	0,54
9	89,5	92–3	68,10	7,40	$C_{37}H_{48}O_{10}$	68,25	7,37	0,59
10	91,2	41–2	68,28	7,40	$C_{38}H_{50}O_{10}$	68,47	7,57	0,60

TABLE 4. 4,4'-(alkylenedioxy)diphenylsuccinic Acids (III)

n	Yield, %	mp, °C	Found, %		Molecular formula	Calculated, %		R_f (B)
			C	H		C	H	
1	79,40	90—2	58,53	4,70	$C_{21}H_{20}O_{10}$	58,33	4,63	0,23
2	80,40	125—8	59,12	5,19	$C_{22}H_{22}O_{10}$	59,19	4,93	0,24
3	84,56	212—15	59,04	5,66	$C_{23}H_{24}O_{10}$	60,00	5,21	0,24
4	85,05	173—5	60,30	5,84	$C_{24}H_{26}O_{10}$	60,75	5,49	0,25
4 (—CH(CH$_3$) (CH$_2$)$_2$)	85,50	188—90	61,19	5,47	$C_{24}H_{26}O_{10}$	60,76	5,48	0,25
5	86,50	139—40	64,35	6,10	$C_{25}H_{28}O_{10}$	64,12	5,97	0,30
6	86,70	90—5	62,13	5,68	$C_{26}H_{30}O_{10}$	62,15	5,97	0,31
7	87,30	160—3	62,61	6,30	$C_{27}H_{32}O_{10}$	62,78	6,24	0,31
8	87,95	138—40	62,98	6,64	$C_{28}H_{34}O_{10}$	63,38	6,46	0,32
9	88,05	108—10	62,82	6,55	$C_{28}H_{34}O_{10}$	63,97	6,63	0,32
10	89,50	83—5	64,92	7,00	$C_{30}H_{38}O_{10}$	64,50	6,85	0,32

to give the α,ω-haloalkoxybenzaldehydes (Table 2). IR spectrum, ν, cm^{-1}: 1695-1700 (C=O).

α,β-Bis-(4-formylphenoxy)ethane [6]. To a mixture obtained by adding dropwise 67.54 g (0.44 mole) of phosphoryl chloride to 48.18 g (0.66 mole) of DMF at 70-72°C was added 23.5 g (0.11 mole) of α,β-diphenoxyethane [12]. The mixture was heated on the boiling water bath for 12 h, and after cooling it was poured into ice water, and basified with saturated sodium carbonate solution. The crystals which separated were filtered off and recrystallized from 50% ethanol, mp 117-118°C. Yield 9.1 g (30%), R_f 0.19 (A). IR spectrum, ν, cm^{-1}: 1695 (C=O).

Tetraethyl α,ω-Alkylenebis(oxybenzylidenemalonates) (II) [8]. A mixture of 0.195 mole of (I), 62.4 g (0.4 mole) of ethyl malonate, 0.2 g of piperidine, 4 ml of glacial acetic acid, and 500 ml of dry benzene was boiled in a flask fitted with a water separator until no more water separated (3.5 ml). The benzene was removed from the reactive mixture under reduced pressure, and to the residue was added 200 ml of water. The mixture was extracted with ether, the extracts dried over sodium sulfate, and the ether removed, when the residue crystallized, and was recrystallized from 50% alcohol (Table 3). IR spectrum, ν, cm^{-1}: 1630-1650 (C=C), 1740-1755 (C=O).

4,4'-(α,ω-Alkylenedioxy)diphenylsuccinic Acids (III) [10]. A mixture of 0.16 mole of (II), 31.4 g (0.64 mole) of sodium cyanide in 100 ml of water and 200 ml of ethanol was heated on the water bath for 2 h. After removal of the solvent under reduced pressure, 47.4 g (0.96 mole) of sodium hydroxide in 100 ml of ethylene glycol was added. Heating was continued for 40 h, the glycol removed, and to the residue was added 100 ml of water followed by extraction with ether. The aqueous layer was filtered with charcoal, and acidified with hydrochloric acid. The solid which separated was filtered off, and recrystallized from dilute acetic acid (1:10) (Table 4). IR spectrum, ν, cm^{-1}: 1710-1725 (C=O).

4,4'-(α,ω-Alkylenedioxy)diphenylsuccinimides (Va-m) [8]. A mixture for 5 g of (III) and 50 ml of acetic anhydride was heated on the water bath for 6 h, and after removal of acetic acid and acetic anhydride the residue was dissolved in dry ethyl acetate. To this solution was added a saturated solution of ammonia in ethyl acetate until an alkaline reaction was obtained. After standing for 2 h, the salt (VI) was filtered off and transferred to a round-bottomed flask. The temperature of the flask contents was brought to 200-220°C, and heating continued at this temperature for 1 h. The resulting glassy solid was recrystallized from methanol (Table 5). Similarly obtained was N-methyl-4,4'-(α,ω-butylenedioxy)diphenylsuccinimide (Vf), using ethyl acetate saturated with methylamine instead of ammonia. IR spectrum, ν, cm^{-1}: 1680, 1710, 1735, 1780 (C=O), 3200 (NH) (broad band). The molecular ion peaks were in agreement with the molecular masses of (Va-m).

4,4'-(Methylenedioxy)diphenylsuccinimide (Va). A mixture of 22.5 g (0.042 mole) of (II, n = 1) in 200 ml of absolute ethanol and 4.1 g (0.084 mole) of sodium cyanide in 20 ml of water was heated for 18 h at 65-75°C After removal of the alcohol, the residue was treated with 200 ml of water and extracted with ether. The ether layer was dried over sodium sulfate, and the ether removed. The resulting diethyl 4,4'-(methylenedioxy)diphenyl-β-cyanopropionate (VI) was recrystallized from ethanol (1:1). Yield, 5 g (28.44%), mp 82°C, R_f 0.403 (A). Found, %: C 67.15; H 6.06; N 6.27. Calculated, %: C 66.66; H 5.77; N 6.22.

The aqueous layer was filtered with charcoal, and acidified with hydrochloric acid. The oily mixture of 4,4'-(methylenedioxy)diphenylsuccinamic acid (VII) and 4,4'-(methylenedioxy)-diphenylsuccinic acid (III, n = 1) was extracted with ethyl acetate; ethyl acetate saturated with ammonia was added until basified. After standing for 2 h, the ethyl acetate was distilled off, and the residue [a mixture of salts (IV, n = 1, R = H) and (VIII)] was subjected to cyclization at 200-210°C. The resulting glassy solid (Va) was recrystallized from methanol (Table 5).

TABLE 5. 4,4'-(α,ω-Alkylenedioxy)diphenylsuccinimides (Va-m)

Compound	Yield, %	mp, °C	Found, %			Molecular formula	Calculated, %			R_f (B)
			C	H	N		C	H	N	
a	50,00	120—1	63,65	4,32	6,81	$C_{21}H_{18}O_6N_2$	63,63	4,57	7,10	0,52
b	52,00	198—200	64,67	4,64	6,32	$C_{22}H_{20}O_6N_2$	64,70	4,90	6,86	0,53
c	55,20	150—1	65,19	5,01	6,90	$C_{23}H_{22}O_6N_2$	65,70	5,21	6,63	0,54
d	55,50	114—5	65,58	5,25	6,20	$C_{24}H_{24}O_6N_2$	66,05	5,50	6,42	0,59
e	57,50	175—7	66,68	5,55	6,10	$C_{25}H_{26}O_6N_2$	66,20	5,28	6,48	0,60
f	58,20	142—3	67,27	6,21	6,19	$C_{26}H_{28}O_6N_2$	67,24	6,03	6,03	0,60
g	60,20	134—5	66,75	5,30	5,91	$C_{25}H_{24}O_6N_2$	66,66	5,78	6,22	0,61
h	60,50	145—7	67,61	6,11	5,31	$C_{28}H_{32}O_6N_2$	67,82	5,25	6,08	0,62
i	90,00	—	—	—	—	$C_{28}H_{30}O_6N_2Na_2$	—	—	—	—
j	61,80	87—8	66,30	6,50	5,99	$C_{27}H_{30}O_6N_2$	67,80	6,26	5,84	0,64
k	63,00	78—9	68,67	6,30	5,70	$C_{28}H_{32}O_6N_2$	68,27	6,55	5,69	0,69
l	64,50	79—80	68,77	6,71	5,53	$C_{29}H_{34}O_6N_2$	68,96	6,70	5,55	0,71
m	67,55	108—9	69,49	7,16	5,78	$C_{30}H_{36}O_6N_2$	69,21	6,97	5,38	0,74

TABLE 6. Anticorazole Activity of 4,4'-(α,ω-Alkylenedioxy)-diphenylsuccinimides (Va, d-f, h, i, m)

Compound	Antagonism to corazole, ED_{50}, mg/kg
Va	660 (507,6—858)
Vd	580 (495,7—672,8)
Vf	780 (410,5—1482)
Ve	470 (293,7—752)
Vh	120 (72,7——198)
Vi	170 (85—340)
Vm	135 (79,3—159,5)
Pufemid	86 (58,1——127,3)

Sodium Salt of 4,4'-(α,ψ-Hexylenedioxy)diphenylsuccinimide (Vi). To the alkoxide obtained from 0.23 g (0.01 mole) of metallic sodium and 200 ml of absolute methanol was added 4.6 g (0.01 mole) of (Vi, n = 6) dissolved in 100 ml of absolute methanol. After keeping for 2 h, the solid which separated was filtered off and dried at room temperature and recrystallized from absolute methanol. The purity was checked by titrating for sodium ion in aqueous chloroform (95.5%).

EXPERIMENTAL PHARMACOLOGY

Succinimides (Va-m) were tested for anticonvulsant activity in 545 white mice weighing 18-25 g. Each group comprised 5-15 animals. The compounds were administered intraperitoneally as suspensions with methylcarboxycellulose. The controls were treated with the emulsifier.

Anticorazole activity, elimination of the effects of maximum electroshock, nicotine, and arecoline, side effects (disturbance of motor coordination and myorelaxation), and the acute toxicities of the compounds were determined by the methods described in [13].

For comparison, pufemid (p-isopropoxyphenylsuccinimide) [14] was used. The effective (ED_{50}) and neurotoxic (TD_{50}) doses were calculated, together with the therapeutic index, LD_{50}/ED_{50} [15].

It was found that treatment with most of the compounds caused disturbance of respiratory coordination, ataxia, and death in 50% of the animals at doses of approximately 1500 mg/kg. In addition, the compounds has virtually no effect on nicotine convulsions, arecoline tremor, and tonic extension due to maximum electroshock. Most of the compounds showed anticorazole activity in subtoxic doses (Table 6), although (Vb, c, g, j-l) were completely devoid of this activity. Exceptions were (Vh, m), which had higher anticorazole activity (Table 6). The TD_{50} of the test compounds was 500 mg/kg, and the LD_{50} 750 mg/kg. The therapeutic indices of (Vh, m), which give a measure of the safety of the anticonvulsants, were 6.2 and 5.5, respectively. The test compounds were markedly inferior to pufemid, which has a therapeutic index of 25.

This study has therefore shown that (Vh, m) have the highest anticorazole activity of the compounds tested.

Replacement of the hydrogen atoms on the nitrogen atoms of the disuccinimides by sodium or the methyl group, as in the case of pufemid, reduces anticonvulsant activity.

These results indicate that the active centers in the receptors which interact with the succinimides appear to be located side by side at a distance approximately equal to the lengths of the hexamethylene and decamethylene chains. A similar conclusion was reached previously in a study with polymethylene disquaternary ammonium salts [16]. In brackets are given the confidence internals for P = 0.05 [16], from which it will be seen that the maximum ganglion-blocking activity occurs at the distance of six methylene groups between the quaternary nitrogens, and the maximum curariform activity at a distance of ten methylene groups, i.e., in decamethylene bistrimethylammonium bromides.

LITERATURE CITED

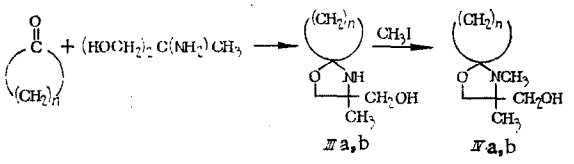
1. S. A. Avetisyan and O. L. Mndzhoyan, Arm. Khim. Zh., 24, No. 2, 137-145 (1971).
2. N. E. Akopyan and D. A. Gerasimyan, Biol. Zh. Arm., 24, No. 2, 91-94 (1971).
3. A. Albert, Selective Toxicity [in Russian], Moscow (1971), p. 68.
4. W. P. Neisch, Rec. Trav. Chim., 66, 433-442 (1947).
5. Z. Gatterman, Justus Liebigs Ann. Chem., 357, 313-383 (1907).
6. G. Baddeley and M. A. Vickars, J. Chem. Soc., 765-770 (1963).
7. O. L. Mndzhoyan, S. A. Avetisyan, and N. S. Nesunts, Zh. Prikl. Khim., 55, No. 1, 221-224 (1982).
8. S. A. Avetisyan and O. L. Mndzhoyan, Arm. Khim. Zh., 23, No. 4, 355-364 (1970).
9. J. R. Geigy, Jpn. Pat. No. 6610370 (1967); Chem. Abstr., 67, 22492 (1967).
10. O. L. Mndzhoyan, S. A. Avetisyan, L. V. Azaryan, et al., Arm. Khim. Zh., 29, No. 11, 948-951 (1976).
11. S. A. Avetisyan and O. L. Mndzhoyan, Arm. Khim. Zh., 24, No. 3, 252-258 (1971).
12. V. Solonin, Zh. Russ. Fiz. Khim. O-va., 30, 607-632 (1898).
13. L. V. Azaryan, S. A. Avetisyan, N. E. Akopyan, et al., Khim.-farm. Zh., No. 8, 55-58 (1978).
14. D. A. Gerasimyan and N. E. Akopyan, in: Conference on the Antiepileptic Drug Pufemid. Proceedings [in Russian], Erevan (1980), p. 14.
15. J. T. Litchfield and F. Wilcoxon, J. Pharmacol. Exp. Ther., 96, 99-104 (1949).
16. W. D. M. Paton, J. Pharm. Pharmacol., 1, 273-286 (1949).

SYNTHESIS OF SPIROCYCLIC OXAZOLIDINES AND THEIR EFFECTS ON PHYSICAL WORK CAPACITY

K. A. Gevorkyan, G. L. Papayan, É. A. Shirinyan, T. K. Atayan, and A. S. Vorskanyan

UDC 615.214.31:547.787].012

2-Amino-2-methylpropane-1,3-diol aspartate (I) is known to improve physical work capacity in experimental situations. We have synthesized some spirocyclic 2-amino-2-methylpropane-1,3-diols, and examined their effects on the work capacity of the body when subjected to a combination of extreme factors.



Prolonged boiling of a benzene solution of cyclopentanone or cyclohexanone with the diol (II) in the presence of catalytic amounts of p-toluenesulfonic acid afforded 2-spirocyclopentyl- and 2-spirocyclohexyl-4-methyl-4-hydroxymethyl-1,3-oxazolidine (IIIa, b), re-

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 7, pp. 806-808, July, 1983. Original article submitted March 2, 1982.

0091-150X/83/1707-0484$07.50