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

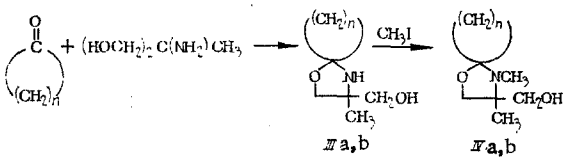
1. S. A. Avetisyan and O. L. Mndzhoyan, Arm. Khim. Zh., 24, No. 2, 137-145 (1971).
2. N. E. Akopyan and D. A. Gerasimyan, Biol. Zh. Arm., 24, No. 2, 91-94 (1971).
3. A. Albert, Selective Toxicity [in Russian], Moscow (1971), p. 68.
4. W. P. Neisch, Rec. Trav. Chim., 66, 433-442 (1947).
5. Z. Gatterman, 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

spectively. The IR spectra of these compounds showed absorption for the primary hydroxyl group (3000-3200 cm^{-1}). The PMR spectra showed singlets for CH_3 (1.2 ppm) and ONH (3.1 ppm), and signals for the hydrocarbon ring (1.4-1.7 ppm) and the OH group (3.4 ppm).

Reaction with methyl iodide followed by treatment of the resulting hydroiodides with alkali gave the corresponding N-methyl derivatives (IVa, b). The PMR spectra of the latter contained no signals for NH, but a singlet for NCH_3 appeared (2.2 ppm).

Bases (IIIa, b) and (IVa, b) were converted into their hydrochlorides.

EXPERIMENTAL CHEMISTRY

TLC was carried out on Silufol UV-254 plates in the solvent system methanol–33% aqueous dimethylamine (10:1), developed with iodine vapor.

IR spectra were obtained on a UR-20 spectrophotometer (East Germany) in vaseline oil. Mass spectra were obtained on an MX-1320 instrument with direct introduction of the sample into the ionization region, ionizing electron energy 60-65 eV, temperature range 40-50°C. PMR spectra were obtained on a Varian T-60 spectrometer in CCl_4, internal standard TMS. Melting points were determined on a Boezius (East Germany) micro-hot plate.

2-Spirocyclopentyl-4-methyl-4-hydroxymethyl-1,3-oxazolidine (IIIa). A solution of 21 g (0.25 mole) of cyclopentanone and a catalytic amount of p-toluenesulfonic acid in 320 ml of benzene was boiled for 2 h with a water separator. 2-Amino-2-methylpropane-1,3-diol (II) (26.77 g, 0.255 mole) was then added, and boiling continued for 48 h, when 4.2 ml of water was separated. Following removal of the solvent, the residue was distilled under reduced pressure to give 41.1 g (96%), bp 122-123°C (5 mm), d_4^{20} 1.0886, n_D^{20} 1.4851, R_f^+ 0.50. Found, %: C 63.26; H 9.60; N 8.56. $C_9H_{17}NO_2$. Calculated, %: C 63.13; H 10.10; N 8.17. Mass spectrum, m/e: 171(15) M^+, 142(100), 123(13), 112(73), 84(14). Hydrochloride, mp 117-118°C. Found, %: Cl 17.30. $C_9H_{18}ClNO_2$. Calculated, %: Cl 17.07.

2-Spirocyclohexyl-4-methyl-4-hydroxymethyl-1,3-oxazolidine (IIIb). Similarly, from 4.9 g (0.05 mole) of cyclohexanone and 5.75 g (0.055 mole) of (II) there was obtained 7.5 g (81%) of (IIIb), mp 51-53°C, R_f 0.55. Found, %: C 65.00; H 10.09; N 7.63. $C_{10}H_{19}NO_2$. Calculated, %: C 64.83; H 10.34; N 7.56. Mass spectrum, m/e: 185(85) M^+, 154(100), 142(73), 129(47), 112(42), 98(18). Hydrochloride, mp 105-107°C. Found, %: Cl 15.80. $C_{10}H_{20}ClNO_2$. Calculated, %: Cl 15.92.

2-Spirocyclohexyl-3,4-dimethyl-4-hydroxymethyl-1,3-oxazolidine (IVb). A solution of 4 g of (IIIb) in 15 ml of freshly distilled methyl iodide was kept at room temperature in a dark flask for four days. Excess methyl iodide was removed at room temperature under reduced pressure. The crystals were washed several times with dry ether, filtered, and dried to give 6.4 g (90%) of (IVb) hydroiodide, mp 159-160°C, raised by crystallization from alcohol to 167-168°C. Found, %: C 40.42; H 7.13; N 4.41; I 38.69. $C_{11}H_{22}INO_2$. Calculated, %: C 40.38; H 6.77; N 4.28, I 38.78. Treatment of the hydroiodide with alkali gave the free base (IVb), which was used without further purification. Yield quantitative, n_D^{20} 1.4910, R_f 0.50. Found, %: C 66.48; H 10.54; N 7.17. $C_{11}H_{21}NO_2$. Calculated, %: C 66.29; H 10.62; N 7.03. Mass sectrum, m/e: 199(58) M^+, 185(15), 168(100), 154, 156(98), 143(20), 137(16), 126(20), 112(85), 98(8). Hydrochloride, mp 178-179°C. Found, %: Cl 15.03. $C_{11}H_{22}ClNO_2$. Calculated, %: Cl 15.03.

2-Spirocyclopentyl-3,4-dimethyl-4-hydroxymethyl-1,3-oxazolidine (IVa). Similarly obtained was hydroiodide (IVa), yield 85%, mp 92-93°C. Found, %: C 37.98; H 6.80; N 4.28; I 40.60. $C_{10}H_{20}INO_2$. Calculated, %: C 38.35; H 6.43; N 4.47; I 40.52. The hydroiodide was converted in quantitative yield into free base (IVa), mp 58-59°C. R_f 0.70. Found, %: C 65.52; H 9.96; N 7.76. $C_{10}H_{19}NO_2$. Calculated, %: C 64.82; H 10.25; N 7.56. Mass spectrum, m/e: 185(90) M^+, 170(32), 156, 154(60), 143(39), 126(100), 112(72), 86(100). Hydrochloride, mp 161-162°C. Found, %: Cl 15.90. $C_{10}H_{20}ClNO_2$. Calculated, %: Cl 15.99.

EXPERIMENTAL BIOLOGY

Pharmacological examination of the compounds was carried out using tests designed to assess enhancement of the tolerance of the body to the effects of stress factors. The standards used for comparison were amphetamine and pyridrol, which stimulate psychic and physical activity, together with (II) and its salts, and (I) and its hydrochloride.

The tests were carried out on white male rats weighing 130-150 g. The compounds were dissolved in distilled water and administered intraperitoneally in a single dose of volume

TABLE 1. Effects of 2-Amino-2-methylpropane-1,3-diol (II), Oxazolidines (IIIa, b) and (IVa, b), Their Salts, Amphetamine, and Pyridrol on the Physical Endurance of Rats Subjected to a Combination of Stresses [times of onset of total muscular fatigue given (as a % of the control, M ± m)]

Compound	Dose, mg/kg intraperitoneal					
	1,5	2,0	5,0	10,0	20,0	50,0
Hydrochloride IIIa	0	—	+10±10	−28±10	—	−35±8*
Hydrochloride IIIb	—	—	+38±9*	—	+45±13*	0
IVa	—	—	+10±7	+10±12	−22±12	—
IVb	—	0	+18±9	+10±4	−10±10	—
Hydrochloride IVa	—	—	0	+18±8	+18±11	0
Hydrochloride IVb	—	—	0	0	—	−20
II	—	—	−10±7	0	—	0
I	—	—	+20±8	+30±4*	−10±4	—
Hydrochloride II	0	—	+29±10*	+12±13	—	—
Amphetamine	+20±8*	+47±12*	−10±10	−28±7*	—	—
Pyridrol	+42±14*	+14±10	−30±8*	—	—	—

Note. The signs (+) and (−) denote an increase or decrease in endurance. Asterisks indicate statistically significant differences ($P < 0.05$). Each figure represents the result obtained from 7-10 animals.

0.5 ml one hour before the test. The effects of the compounds on work capacity of animals under extreme conditions (muscular work, antiorthostatic loading, and hypothermia) were assessed by a previously described method [2]. The results were treated statistically, using the t criterion [3]. The experimental results are shown in Table 1. In subsequent studies, the effects of hydrochloride (II) were studied on a number of pharmacological factors in comparison with amphetamine and pyridrol, viz., arterial pressure, pulse rate and respiration, rectal temperature (in rats), tonus of the third eyelid and arterial pressure in cats of weight 2-3 kg narcotized with nembutal [4]. Also examined were effects on peripheral sympathetic nerves and adrenoreceptors, as determined by the changes in the contractions of the vas deferens induced by transmural electrical stimulation and by adrenalin [5].

It will be seen from Table 1 that of the heterocyclic compounds obtained, only hydrochloride (IIIb) increased the physical endurance of the animals. In a dose of 20 mg/kg, its stimulant effect was as great as that of amphetamine and pyridrol, and exceeded that of aspartate (I) and hydrochloride (II). Hydrochloride (II) was somewhat less active.

The studies showed that hydrochloride (IIIb) by the intravenous route, either in a dose of 20 mg/kg, or in doses exceeding those required to increase physical work capacity (50-100 mg/kg), did not cause in rats any significant changes in arterial pressure, body temperature, pulse rate, or respiration, and in doses of 5 and 50 mg/kg it had no effect on arterial pressure and the nictitating membrane reaction in cats. In the case of amphetamine and pyridrol, changes in these parameters were observed even at doses of one half the effective dose for increased endurance.

Unlike amphetamine and pyridrol hydrochloride (IIIb) in a final concentration of 0.05 and 0.5 μmole/ml did not affect the amplitudes of the contraction of rat vas deferens, i.e., it had no effect on the postgangliar sympathetic nerves and adrenoreceptors. At these concentrations, amphetamine and pyridrol exerted typical adrenomimetic activity.

The acute toxicities in mice were determined intraperitoneally, and calculated graphically [3].

It was found that the LD_{50} of hydrochloride (IIIb) was 3700 (3472-4050) mg/kg, aspartate (I) 1900 (1750-2150) mg/kg, amphetamine 137 (126-194) mg/kg, and pyridrol 117 (96-143) mg/kg,

Thus, spirocyclic oxazolidines have been found to include biologically active compounds of low toxicity, which increase bodily tolerance to the joint effects of extreme factors, and differ in their spectrum of pharmacological effects from known stimulants of psychic and physical activity.

LITERATURE CITED

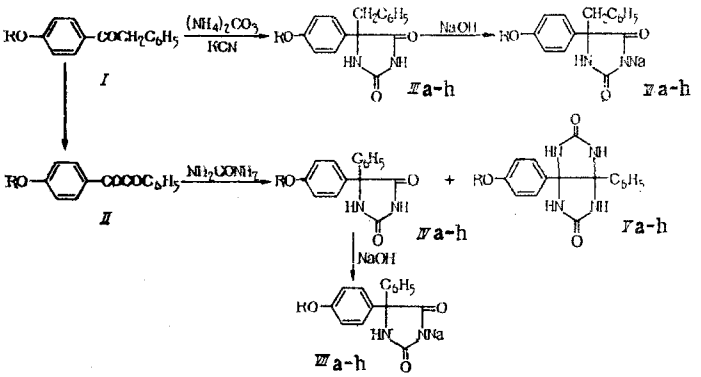
1. French Pat. No. 1300M; Chem. Abstr., 57, 1525g (1962).
2. O. M. Avakyan and É. A. Shirinyan, Byull. Eksp. Biol., No. 10, 375 (1977).
3. M. L. Belen'kii, Fundamentals of the Quantitative Evaluation of Pharmacological Effects [in Russian], Riga (1959), pp. 13, 71.
4. O. M. Avakyan, Biol. Zh. Armenii, 21, 8 (1968).
5. O. M. Avakyan, Pharmacological Regulation of the Release and Capture of Adrenalin [in Russian], Erevan (1973), p. 55.

5-p-ALKOXYPHENYL-5-BENZYL- AND 5-p-ALKOXYPHENYL-5-PHENYLHYDANTOINS AND THEIR SODIUM SALTS

L. V. Azaryan, O. L. Mndzhoyan, S. A. Avetisyan, N. E. Akopyan, I. A. Dzhagatspanyan, and A. G. Akopyan

UDC 615.213.547.783].074:543.544

In continuation of earlier studies on hydantoin derivatives [1], some 5-p-alkoxyphenyl-5-benzyl- (III) and 5-p-alkoxyphenyl-5-phenylhydantoins (IV) have been synthesized together with their sodium salts (VI, VII), and their anticonvulsant properties examined. The compounds (III) were obtained by the Bucher-Berg reaction [2], and (IV) by condensing 5-substituted benzils (II) with urea, as follows:



III, IV, V, VI, VII: a) R = CH_3; b) R = C_2H_5; c) R = C_3H_7; d) R = iso-C_3H_7; e) R = C_4H_9; f) R = iso-C_4H_9; g) R = C_5H_{11}; h) R = iso-C_5H_{11}.

There is contradictory information in the literature on the preparation of the benzils (II) by oxidation of p-isoalkoxydesoxybenzoins, (I) with selenium dioxide. According to [4], the yields of benzils do not exceed 15%, whereas the yields reported in [5] are 76-96%. The results of our own experiments on the oxidation of p-isoalkoxydesoxybenzoins are in accordance with [4]. Oxidation of p-isoalkoxydesoxybenzoins gave, in addition to p-isoalkoxybenzils, p-hydroxybenzil, p-desoxyhydroxybenzoin, and o-isoalkoxydesoxybenzoin (by TLC). For this reason, the o-isoalkoxybenzils were prepared by alkylation of p-hydroxybenzil with the appropriate alkyl halides.

EXPERIMENTAL CHEMISTRY

TLC was carried out with bound layers of KSK silica gel–gypsum using the mobile phases: a) benzene–ethyl acetate–acetic acid (7:3:1), developer phosphomolybdic acid (5% alcoholic solution), developing temperature 60-70°C [6]; b) ether–light petroleum (3:2), developer iodine vapor; and c) chloroform–methanol (10:1), developer bromocresol purple.

IR spectra were obtained on a UR-20 spectrometer (East Germany). Mass spectra were obtained on an MX-1320 mass spectrometer with direct introduction of the sample into the ion

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. 808-813, July, 1983. Original article submitted July 29, 1982.

0091-150X/83/1707-0487$07.50