SYNTHESIS, ANALGESIC, AND CEREBROVASCULAR ACTIVITY OF N-AMINOACETYL DERIVATIVES OF PYROLLIDONE-2

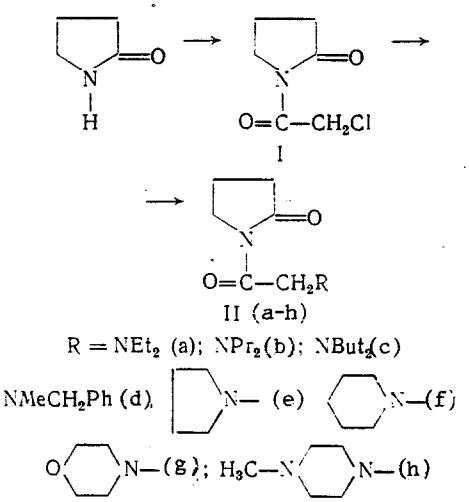
L. M. Kostochka, S. E. Mochalovskii,
I. V. Chernyakova, T. S. Gan'shina,
A. P. Skoldinov, V. N. Zhukov,
and R. S. Mirzoyan

UDC 615.211+615.224]:547.745].012.1

The presence of analgesic activity in certain GABA derivatives [3, 6] is indicated by the participation of a GABA-ergic system in the regulation of pain sensitivity. GABA-ergic mechanisms play a significant role in the regulation of cerebral blood circulation [1, 2]. In that connection, we synthesized a number of N-aminoacetyl derivatives of pyrollidone-2 for the purpose of identifying compounds with analgesic and cerebral vascular activity.

The compounds we synthesized would seem to represent a dipeptide of a cyclic GABA and a substituted glycine. The latter is part of the pentapeptides of leu- and met-enkephalins which exhibit analgesic activity.

The chloroacetyl derivative of pyrollidone-2 (I) is obtained at a good yield (84.2%) by acylating pyrollidone-2 with chloroacetyl chloride.



The corresponding N-aminoacyl derivatives of pyrollidone-2 (IIa-h, Table 1) were obtained by the slow (4 h) addition of a mixture of 1 equivalent of secondary amine and 1 equivalent of triethylamine in benzene to a solution of I in benzene. When the reagents are stirred rapidly a partial substitution of the pyrollidine ring by an amine takes place along with the formation of the IIa-h amination products which results in the formation of the corresponding glycine amide $R_2NCH_2CONR_2$ (III). In some cases this side reaction cannot be avoided even when the amine is introduced slowly. Thus, when compound I was reacted with N-methylpiperazine a 6% side product of IIIg with M^+-240 was detected in the reaction mixture by chromato-mass spectrometry. When compound I reacted with pyrollidone, there was a 13% formation of the side product IIIe.

One should note that in our attempt to aminate N-chlorobutyrylpyrollidone-2 with morpholine the morpholine-substituted pyrollidine ring was the principal product. This indicates the variable reactability of these compounds in a nucleophilic substitution reaction.

Scientific-Research Institute of Pharmacology, USSR Academy of Medical Sciences, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 22, pp. 406-409, April, 1989. Original article submitted February 10, 1988.

0091-150X/89/2304-0291 $12.50

TABLE 1. N-(Aminoacetyl)pyrollidones-2 (IIa-h)

Compound	Yield, %	bp. °C	mp, °C	Empirical formula (oxalates)	M+
IIa	60,6	(105—110)/1 mm	161—3	$C_{10}H_{18}N_2O_2 \cdot C_2H_2O_4$	198
IIb	51,9	(129—131)/1 mm	132—4	$C_{12}H_{22}N_2O_2 \cdot C_2H_2O_4$	226
IIc	40,7	(135—140)/1 mm	128—30	$C_{14}H_{26}N_2O_2 \cdot C_2H_2O_4$	254
IId	61,8	(173—174)/1 mm	165—7	$C_{14}H_{18}N_2O_2 \cdot C_2H_2O_4$	246
IIe	33,5	148/2 мм mm	122—5	$C_{10}H_{16}N_2O_2 \cdot C_2H_2O_4$	196
IIf	59,3	(137—140)/1 mm	177—80	$C_{11}H_{18}N_2O_2 \cdot C_2H_2O_4$	210
IIg	50,3	(149—150)/1 mm*	160—2	$C_{10}H_{16}N_2O_2 \cdot C_2H_2O_4$	212
IIh	43,7	(146—147)/1 mm**	168—70	$C_{11}H_{19}N_3O_2 \cdot 1{,}25C_2H_2O_4$	225

*Base $C_{10}H_{16}N_2O_3$.
**Base $C_{11}H_{19}N_3O_2$.

TABLE 2. Analgesic Action and Acute Toxicity of N-Aminoacyl Derivatives of Pyrollidone-2

Compound	Dose, mg/kg	Analgesic action (in %) by tests			Acute toxicity, LD_{50}, mg/kg
		1	2	3	
IIa	46,0	38,8*	76,7**	22,5	460,0
IIb	45,0	27,7*	41,7**	15,0	450,0
IIc	43,0	30,2*	71,7*	17,5	430,0
IId	47,5	27,5*	38,3**	30,0	475,0
IIe	43,0	16,4	73,3**	17,6	430,0
IIf	36,0	69,8*	40,0*	17,5	360,0
IIg	200,0	12,6	23,3*	117,5	2000
IIh	200,0	28,4	66,7*	137,5**	2000
Morphine	3,0	100,0***	100,0***	100***	345,0

Note: 1 is "tail contraction" test; 2 is "hot plate" test; 3 is "pressure on tail" test. Average values are given for six experiments. Asterisks signify statistically significant differences from control (here and in Table 3): one — $P < 0.05$, two — $P < 0.01$, three — $P < 0.001$. Morphine at a dose of 3 mg/kg was taken as 100% analgesia.

EXPERIMENTAL CHEMICAL

Mass spectra were recorded on a Varian MAT-112 instrument at 70 eV; temperature of the ionization chamber was 250°C. Substance purity was assayed on a Tsvet-152 chromatograph (column length 0.7 m, diameter 4 mm, solid carrier was Chromaton N-AW 0.25 mm, liquid phase SE-30/5%). Specifications: evaporator temperature 300°C, temperature program 75-250°C, 10° per min, nitrogen consumption 60 ml per min.

Melting point was determined on a Bötius microheating instrument. Element analysis results coincided with the calculated values.

N-Chloroacetylpyrollidone-2 (I). A 60 g portion of chloroacetyl chloride dissolved in 50 ml benzene was added dropwise to a solution of 90.3 g of pyrollidone-2 in 200 ml of benzene. When the addition was completed the mixture was boiled for 2 h. The pyrollidone-2 chlorohydrate which precipitated upon cooling was filtered off, the benzene was distilled off, and the residue was vacuum-redistilled which left the fraction with a bp of 115-118°C/1 mm. Yield of I was 72 g (84.2%). $C_6H_8NO_2$.

Synthesis of N-Aminoacetyl Derivatives of Pyrollidone-2 (IIa-h standard method). A mixture of 0.03 mole of the corresponding secondary amine and 0.03 mole of triethylamine dissolved in 20 ml of benzene was added dropwise upon boiling over a 4 h period to a solution of 0.03 mole of compound I in 30 ml of benzene. The precipitated triethylamine chlorohydrate was filtered off, the solvent was distilled off, and the oily residue was vacuum-redistilled. The resultant product was dissolved in a small quantity of abs. alcohol to which a computed amount of oxalic acid dissolved in dry ether was added. The resultant oxalate was filtered off and dried in a dessicator.

TABLE 3. Effect of N-Aminoacetyl Derivatives of Pyrollidone-2 on the Analgesic Action of Morphine (M)

Compound	Analgesic action (in %) by tests		
	1	2	3
M + IIa	76,7**	80,0*	37,5
M + IIb	143,1***	75,0***	117,5***
M + IIc	29,3*	88,3***	47,5*
M + IId	106,9***	118,3***	72,5**
M + IIe	43,1***	131,6***	90,0*
M + IIf	69,8***	45,0*	37,6
M + IIg	67,2***	138,3***	110,0**
M + IIh	58,6***	93,3*	127,5***
M	100,0	100,0	100,0

EXPERIMENTAL PHARMACOLOGICAL

An examination was made of the overall action of compounds IIa-h, including acute toxicity, potentiation of subthreshold narcosis and sodium thiopental, analgesic action, and effect on cerebral blood circulation.

Analgesic effect was judged by the following tests: 1) tail contraction on an Analgesia Test instrument (Kern firm, FRG), 2) "hot plate" (55°C) [4], and 3) Randell-Selitto (modified pressure on tail method) on an analgesimeter made by the Ugo Basile firm (Italy) [5].

The tests were made on white mice weighing 18-20 g. Test substances were used at doses equal to $^1/_{10}$ of the LD_{50}. Morphine at a dose of 3 mg/kg was used as the reference.

The cerebrovascular activity of compounds IIa-h was tested on cats under general anesthesia (urethane, chloralose) with artificial lung ventilation. Blood flow into the brain through the carotid artery with careful ligature of the extracranial branches was recorded by a RKE-2BI electromagnetic gauge. Simultaneously readings were made of the arterial pressure in the femoral artery. Recording was made on a Mingograph-81. The compounds were tested at a dose of 10 mg/kg intravenously.

The tested compounds were found to be relatively low in toxicity. Their LD_{50} when administered intravenously to mice was 360-2000 mg/kg (Table 2). Compounds IIa-h exhibit a slight general depressant action and can induce analgesia.

The most active compound in the "tail contraction" test upon thermal nocioceptive stimulation of the tail was compound IIf which has a piperidine radical in its structure.

Compounds IIa, e exhibited rather high activity, although less than that of morphine, in the "hot plate" test.

Compound IIh with a N-methylpiperazine fragment somewhat exceeds the analgesic activity of morphine in mechanical nocioceptive stimulation in the "pressure on the tail" test, but is less effective than morphine in the "hot plate" test. The derivative IIg is less active.

The analgesic action of all the examined substances is completely eliminated by the opiate antagonist naloxone which is indicative of the possible opioidergic mechanism of their action.

The substances IIa-h can both potentiate and attenuate morphine action in nocioceptive stimulation of variable modality (Table 3). Thus, compounds IIb and IId potentiate morphine action in the "tail contraction" test by 43% and 7%, respectively, whereas the remaining compounds of this series attenuate morphine action by 30-70% in this test.

Compounds IIg, IIe, and IId potentiate morphine's analgesic action by 20-40% in the "hot plate" test.

In mechanical nocioceptive stimulation ("pressure on the tail") the most active compounds were IIh, IIb, and IIg, which potentiate the morphine effect by 10-30%. Compounds IIa, IIf, and IIc attenuate morphine action in all the tests by 10-70%.

Thus, a large segment of the examined compounds exhibit a slight naloxone-like action whereas the analgesic activity of some of them is probably mediated by opioidergic mechanisms since that action is eliminated by naloxone.

All of the compounds except IIc and IId intensified cerebral blood circulation in the cats. Compounds IIa, IIf, and IIg exhibited the most pronounced effect on cerebral circulation. Blood flow to the brain under their influence increased by 40%, 36%, and 31%, respectively. Compounds IIa and IIf induced both a reduction and elevation of arterial pressure. As regards IIh, it caused a 14% increase in arterial pressure.

Thus, the examined compounds mainly increase cerebral blood circulation and have variable effects on the level of arterial pressure.

LITERATURE CITED

1. R. S. Mirozyan, Farmakol. Toksikol., 5-14 (1984).
2. T. S. Gan'shina, Byull. Éksp. Biol., No. 10, 439-442 (1980).
3. F. V. De Feudis, Prog. Neurobiol., 19, 1-17 (1982).
4. P. F. Fast and W. J. Potts, Meth. Narcot. Res., 4, 76-77; 101-109 (1975).
5. L. O. Randall and I. I. Selitto, Arch. Int. Pharmacodyn., 11, 409-419 (1957).
6. J. Sawynok, Progr. Neuro-Psychopharmacol. Biol. Psychiat., 8, 581-586 (1984).

CARDIOTROPIC AND PHYSICO-CHEMICAL EVALUATION OF PROXANOLS

S. I. Vorobiyev, E. I. Maevskii,
V. V. Obraztsov, B. I. Islamov,
Yu. V. Ladilov, O. V. Baum, L. A. Popov,
A. A. Safroshkina, and S. V. Eletskaya

UDC 615.384:547.221].014.42.07

Emulsions of perfluorohydrocarbons which are widely used in biomedical research for blood substitution and perfusion preservation of isolated organs are stabilized with the aid of ethylene and propylene block copolymers – proxanols (foreign analogs are called pluronics). The general formula for these block copolymers is $OH(C_2H_4O)_x-(C_3H_6O)_y-(C_2H_4O)x-OH$, where y is the number of polypropylene block chains (POPR); and x is the number of polyethylene block chains (POE). At a certain molecular weight and a POPR/POE ratio of 1:4 the proxanols and pluronics satisfy a number of biomedical requirements, i.e., they readily dissolve in water, exhibit moderate surfactant properties, and have a low toxicity level. Previously completed studies have shown that block copolymers prevent platelet aggregation, raise erythrocyte osmotic resistance, improve the rheological properties of blood, and can effect hemodynamic action due to their colloidal-osmotic properties [5]. We have previously demonstrated that variations in the relative POPR content within a range of 16-22% can be quite significant for biological systems. For example, an increase in the latter suppresses the growth of cultivated lymphoid cells and lowers the LD_{50} in mice [2]. In addition, when high mol. wt. compounds are synthesized for biomedical purposes, possible toxic contaminants must be removed from the proxanols.

The requirements for the emulsion components of perfluorohydrocarbons are considerably more rigid in the manufacture of perfusion media since the isolated organs lack a number of protective, detoxification systems that function in the intact organism. Therefore, we felt that an isolated heart would be a more appropriate object for testing proxanols as components of perfusion media.

In the present study we compared the basic physico-chemical parameters of domestic proxanols 168 and 268 and pluronic F-68 (technical and purified grades) as they affected the intact body as well as an isolated rabbit heart preparation.

Institute of Biophysics, USSR Academy of Sciences, Pushchino.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 22, No. 4, pp. 409-412, April, 1989. Original article submitted March 10, 1988.

0091-150X/89/2304-0294 $12.50