PREPARATION OF 1-[1-OXYL-2,2,6,6-TETRAMETHYL-3,4-DEHYDROPIPERIDYL-4]SILATRANE FOR PHARMACOKINETIC STUDIES

L. P. Petukhov, E. V. Bakhareva,
V. A. Pestunovich, A. B. Shapiro,
P. I. Dmitriev, and M. G. Voronkov

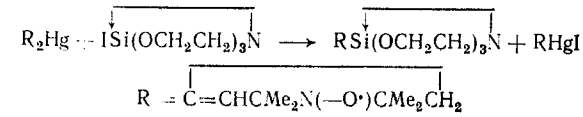
UDC 615.31:547.345].033.07

A broad spectrum of pharmacological activity has recently been discovered for cyclic organosilicon ethers of tris(2-hydroxyalkyl)amines [5-aza-2,8,9-trioxa-1-silabicyclo(3,6,3)-undecanes], known under the abbreviated name of "silatranes" [3]. They favorably affect connecting tissue, blood, CNS, the enzymatic activity, etc. [5, 6]. This was proven by morphological, histological, biochemical and histochemical studies [1, 4]. However, questions of degree of intake of silatranes into the systemic blood circulation from the points of entry, the nature of their distribution in organs and tissues, and their elimination from the organism, have not yet been studied. All these compounds are suitable subjects for pharmacokinetic studies [2, 9].

Experimental pharmacokinetics is based on methods of analytical determination of microconcentrations of medicinal compounds. Silatranes comprise a class of organosilicon compounds for which it is very difficult to select an analytical method for their reliable determination in the multicomponent media of the organism. It appeared to us promising to use for this purpose spin-labeled 1-organylsilatranes, whose distribution in the organism can be easily traced by the EPR method [8]. The most advantageous form of the spin tracer for biologically active compounds are stable radicals containing the $^{\bullet}O-N$ group in a compound with tertiary carbon atoms [10]. These are suitable because of the high stability of radicals of this type.

The EPR method is also "sensitive" to the environment of these N-oxyl radicals, in particular in the case of interaction of the spin tracer with proteins, enzymes, DNA [8].

We found that the synthesis of a spin-labeled silatrane by the classical reaction of a trifunctional silane with tris(2-hydroxyalkyl)amine is not very practicable [11], because of the difficulties in preparation of the initial silanes, derivatives of 2,2,6,6-tetramethyl-4-silyl-3,4-dehydropiperidine or 1-oxyl-2,2,6,6-tetramethyl-4-silyl-3,4-dehydropiperidine. To prepare the first representative of the spin-labeled silatranes, and perhaps of organosilicon N-oxyl compounds in general, we reacted 1-iodosilatrane with bis(1-oxyl-2,2,6,6-tetramethyl-3,4-dehydropiperidyl-4)mercury.



This process is based on the known ability of 1-iodosilatrane to react with organomercury compounds to form 1-organylsilatranes [7]. The end of the reaction was monitored by the EPR method. In the EPR spectrum of the end product a triplet signal is observed (with a 1:1:1 ratio of line intensities), indicating a hyperfine splitting of the unpaired electron with a nucleus of one nitrogen atom, a_N = 17.3 Oe. A quintet EPR spectrum is characteristic of the initial organomercury biradical (ratio of line intensities 1:2:3:2:1), $a_{N_1} = a_{N_2}$ = 8.6 Oe. Therefore, the completion of the reaction can be easily determined from the disappearance of the biradical lines. A mass spectrometric analysis of the reaction product confirmed the formation of the required 1-(1-oxyl-2,2,6,6-tetramethyl-3,4-dehydropiperidyl-4)silatrane (I).

Preliminary results of the examination of the possible use of I in pharmacokinetic studies were obtained as follows. Compound I was administered intravenously to a number of animals (rats) in a dose of 5 mg in 1 ml of physiological solution. At hourly intervals the animals

The Irkutsk Institute of Organic Chemistry, Siberian Branch of Academy of Sciences of the USSR. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 8, pp. 979-981, August, 1986. Original article Submitted May 21, 1985.

 0091-150X/86/2008-0562$12.50

TABLE 1. Distribution of 1-oxyl-2,2,6,6-tetramethyl-3,4-dehydropiperidyl-4) silatrane (I) in Organs and Tissues

Biomaterial	Time after introduction, h			
	1	2	3	4
Blood	+	+	+	+
Liver	—	+	+	+
Spleen	—	+	+	+
Heart	—	+	+	+
Kidneys	—	—	—	+
Muscles	—	—	+	+
Skin	—	—	+	+

Note. +) Detected, —) not detected.

were decapitated, the biomaterial was collected, and its EPR spectrum was recorded. The presence of I in the organs and tissues was indicated by the appearance of an anisotropic signal in the EPR spectrum. The data obtained are listed in Table 1. They show that 2 h after the intravenous administration of I, the latter is detected in blood, liver, spleen and heart, and after 4 h in all the organs and tissues studied, including skin.

Thus, with the EPR method it is possible for the first time to follow the distribution of I as a function of residence time in the organs and tissues of the organism. This makes reliable pharmacokinetic studies of silatranes possible.

EXPERIMENTAL (CHEMICAL PART)

1-(1-Oxyl-2,2,6,6-tetramethyl-3,4-dehydropiperidyl-4)silatrane (I). A 1.78 g portion (3.53 mmoles) of bis(1-oxyl-2,2,6,6-tetramethyl-3,4-dehydropiperidyl-4) mercury is added in a purified argon atmosphere to a degassed solution of 1.05 g (3.53 mmoles) of 1-iodosilatrane in 20 ml of $CHCl_3$. The ampul is evacuated and agitated for 55 h at 20°C. The solvent is evaporated, and the solid residue is dissolved in $CHCl_3$. The solution is filtered and precipitated by heptane. Yield, 0.3 g (40%) of a spin-labeled silatrane I. The EPR spectra were recorded on a RE-1307 spectrometer, with resolving power of 60 mG and sensitivity of $5 \cdot 10^{10}$ spin/G. The mass spectra were obtained on a MX-1307 spectrometer with a direct introduction system at an ionization voltage of 70 eV.

EXPERIMENTAL (BIOLOGICAL PART)

In the experiments male rats weighing 150-180 g each were used. The spin-labeled silatrane was administered intravenously in a dose of 5 mg per ml of physiological solution. In sampling of the biomaterial after the decapitation of the animals, the blood was completely removed by filter paper from the organs studied.

LITERATURE CITED

1. E. V. Bakhareva, M. G. Voronkov, and M. K. Vasil'tsov, Byul. Eksp. Biol., No. 5, 100-101 (1983).
2. M. L. Belen'kii, Elements of Quantitative Evaluation of Pharmacological Effect [in Russian], 2nd edn., Leningrad (1963), pp. 81-106.
3. M. G. Voronkov and G. I. Zelchan, Khim. Geterotsikl. Soedin., No. 1, 51-57 (1965).
4. M. G. Voronkov, E. V. Bakhareva, and I. G. Kuznetsov, Dokl. Akad. Nauk SSSR, No. 3, 736-739 (1982).
5. M. G. Voronkov and V. M. D'yakov, Silatranes [in Russian], Novosibirsk (1978), pp. 107-188.
6. M. G. Voronkov, G. I. Zelchan, and E. Ya. Lukevits, Silicon and Life [in Russian], Riga (1978), pp. 343-392.
7. M. G. Voronkov, V. A. Pestunovich, L. P. Petukhov, and V. I. Rakhlin, Izv. Akad. Nauk SSSR, Ser. Khim., No. 3, 699 (1983).
8. D. J. E. Ingram, Electronic Paramagnetic Resonance in Biology [Russian translation], Moscow (1972), pp. 274-276.
9. K. M. Lakin, Yu. F. Krylov and V. A. Gor'kov, Farmakol. Toksikol. No. 1, 5-16 (1980).
10. Method of Spin Tracers [Russian translation], L. Berliner, ed., Moscow (1979), pp. 207-274.

11. M. G. Voronkov, V. M. D'yakov, and S. V. Kirpichenko, J. Organomet. Chem., 233, 1-147 (1982).

DETERMINATION OF POROUS STRUCTURE PARAMETERS AND SELECTIVITY OF ACETYLCELLULOSE MEMBRANES WITH RESPECT TO DEXTRANS

M. M. Selin

UDC 615.384.012.07

One of the main parameters of the porous structure of membranes which determines their selectivity and permeability is the pore size. The evaluation of the equivalent pore radius ($\bar{r}_{pore}$) according to the permeability of the membranes to water has gained wide acceptance in membrane separation techniques. Since different models are used to describe the membranes and transmembrane transfer of water, it was of interest to compare the $\bar{r}_{pore}$ values obtained for these models.

In the present work we evaluated the pore radius of acetylcellulose ultrafiltration membranes and explored the possibility of determining their selectivity with respect to dextrans according to $\bar{r}_{pore}$ values found.

EXPERIMENTAL

Soviet produced UAM-type acetylcellulose ultrafiltration membranes were studied. With allowance made for different models of semipermeable membranes [1, 17], the $\bar{r}_{pore}$ was calculated according to formulas (1)-(3):

$$\bar{r}_1 = \sqrt{\frac{8 l_W \eta_W d}{W_0 \Delta P}}, \quad (1)$$

where I_W is permeability of the membranes to water [in $cm^3/(cm^2 \cdot sec)$], η_W is viscosity of water [in $(kgf \cdot sec)/cm^2$]; d is membrane thickness (in cm); W_0 is total moisture content of membrane (in wt. %); ΔP is pressure over membrane surface (in MPa).

$$\bar{r}_2 = \frac{\bar{r}_1}{\sqrt{2}} \left(1 + \sqrt{1 + \frac{4\Delta r}{\bar{r}_1 \sqrt{2}}}\right), \quad (2)$$

where $\bar{r}_1$ are values of $\bar{r}_{pore}$ calculated according to (1); Δr is the thickness of the layer bound to water (in nm). For the membranes studied, Δr was taken according to [11]:

$$\bar{r}_3 = \sqrt{\frac{8 l_W \eta_W}{(\xi_0/l)\, \Delta P}}, \quad (3)$$

where ξ_0 is the ratio of the area of the lateral cross section of pores, accessible to transmembrane transfer of water, to the membrane area; l is the length of the membrane pores (in cm).

The permeability of the membranes to water at different pressures was determined on a FM-02-200 ultrafiltration cell. The effective diameter of the membranes was 5.8 cm. To exclude possible deformations under pressure of the porous structure of the membranes studied, the measurements were carried out in the range of 0.01-0.05 MPa according to the method described in [5]. The total moisture content of the membranes (W_0) was determined by difference between moist and dry membranes, according to [3]. The value of ξ_0/l was calculated from the examination of transmembrane diffusion of water [6]. The thickness of the membranes was measured using a micrometer. To calculate the pore radius, mean-arithmetic values of I_W, d, W_0, ξ_0 were used which were experimentally determined for 7 samples of membrane of the same type.

Selectivities of the membranes were determined with an aqueous solution of standard dextran sample with known molecular weight characteristics [12].

All-Union Scientific Research Institute of Technology of Blood Substitutes and Hormonal Preparations, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, No. 8, pp. 985-989, August, 1986. Original article submitted April 5, 1985.

0091-150X/86/2008-0564$12.50