The daily mean toxic doses of 12 oxetanes (Table 2) were measured in mongrel mice of both sexes weighing 18-22 g. The LD_{50} values were calculated using the Litchfield and Wilcoxon method as modified by Rot [1].

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF [α-(2-OXOPYRROLIDINO)ETHYL]TRIETHOXYSILANE

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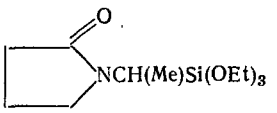
Biologically active organosilicon compounds are currently attracting considerable attention as potential drugs for the treatment of cardiovascular, psychic, oncological, and other diseases. This is due to the important role of silicon in the vital processes of the body, the specific stereoelectronic structure of many biologically active silicon compounds which frequently have no organic analogs, and the great potential opened up to pharmacologists by introducing silicon atoms into biologically active compounds [4].

There is considerable interest in lactams in which a silicon atom is bonded to the N of the heterocycle via a methylene group [2, 3, 5, 9, 10], since these compounds are physiologically active and display biocidal effects [10].

In addition, valuable pharmacological properties are found in lactams which bear carbamidoalkyl groups on the nitrogen. The most active of these was found to be 1-acetamido-2-pyrrolidone, which is the parent of a new group of psychotropic drugs (Novotropil and Pyracetam), and has been used extensively for the treatment of disturbances of the CNS [1].

Continuing these studies, we have obtained the novel [α-(2-oxopyrrolidino)ethyl]triethoxysilane (I) in 73% yield, by hydroxysilylating N-vinyl-2-pyrrolidone with triethoxysilane. The best catalyst for this reaction was found to be acetylacetosodiodicarbonyl. According to PMR and IR spectroscopy, in the presence of this catalyst the reaction proceeds selectively to give the α-adduct only:



EXPERIMENTAL CHEMISTRY

In an ampul was placed a mixture of 39.32 g (0.35 mole) of N-vinylpyrrolidone, 61.18 g (0.37 mole) of triethoxysilane, and 0.65 ml of a 0.01 M solution of acetylacetosodiodicarb-

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onyl in THF ($5.5 \cdot 10^{-5}$ mole/liter). The ampul was cooled, evacuated, sealed, and heated at 150°C for 7 h. Fractionation of the reaction mixture gave 70.7 g (72.6%) of [α-(2-oxopyrrolidino)ethyl]triethoxysilane, bp 116-118°C (2 mm), n_D^{20} 1.4445, MR_D found 70.39, MR_D calculated 71.31. Found, %: C 52.31, H 9.35, N 5.05, Si 9.61. $C_{12}H_{25}NO_4Si$. Calculated, %: C 52.33, H 9.15, N 5.09, Si 10.20.

EXPERIMENTAL PHARMACOLOGY

In order to detect any neurotropic or psychotropic activity, the compound (I) was examined in several tests: 1) acute toxicity (LD_5) by the intraperitoneal route; 2) the spontaneous behavior of the animals in a range of doses from $^1/_4$ to $^1/_{40}$ of the LD_{50}; 3) joint effects with compounds which suppress the CNS (hexobarbital sleep); 4) effects on emotional behavioral reactions; 5) effects on the tonus of the skeletal musculature and the coordination of motor reactions; 6) antishock properties; 7) effects on body temperature; 8) effects on orientational and exploratory activity.

The studies were carried out with white mongrel male mice weighing 20-25 g. In all the tests, the compound was administered intraperitoneally 1 h after the beginning of the experiment.

The acute toxicity following a single dose of (I) was low (the LD_{50} in mice was 2.0 g/kg). In doses close to the LD_{50}, the compound 30-40 min after administration caused considerable suppression of spontaneous motor activity, adynamia, reduction in muscle tonus, and the development of clonic–tonic convolusions with respiratory arrest, followed by death. The spontaneous behavior of animals receiving (I) in doses of 0.05-0.5 g/kg did not differ in any way suggestive of inhibitory or excitatory activity. In all the subsequent tests, therefore, (I) was administered in a dose of 0.05 g/kg ($^1/_{40}LD_{50}$).

To asses the effect of (I) on the duration of hexobarbital sleep, the criterion of the duration of narcosis was the "lateral position" test and the duration of the latent period of narcosis, i.e., the time for which the animals adopted the "lateral position" following administration of the narcotic. The compound reduced by 17% the duration of the latent period of narcosis, and increased by 70% the duration of hexobarbital sleep. The results were statistically significant at $P = 0.05$. Hence (I) potentiates hexobarbital sleep, whereas the compound itself displays neither narcotic nor soporific effects over a wide range of doses (up to toxic levels).

The effect of (I) on emotional behavior reactions was examined by the method of Tedeschi [13], as modified by Polevoi [6]. In a dose of 0.05 g/kg, (I) significantly raised the electrostimulation threshold, and induced the emotional reactions of fear and rage, the threshold for the fear behavioral reaction, however, being raised significantly more ($P < 0.001$).

The effect of (I) on the tonus of the skeletal musculature and motor coordination was assessed by the rotating rod method [11], the roller being rotated at 20 rpm. It was found that, in a dose of 0.05 g/kg, (I) had no significant effect on the tonus of the skeletal musculature, and did not disturb motor coordination in the test animals as compared with the controls.

The effect of (I) on antishock activity was examined using the Electroshock apparatus (Ugo Basile, Italy). The principal shock parameters were chosen to give 100% effect and relatively low mortality (LD_{33}). The duration of electrical stimulation was 1 sec, pulse frequency 100 pulses/sec, impulse duration 0.6 msec, current 16 mA. The antishock activity was assessed by two indices, namely, the percentage of animals which died from the electrical shock, and the length of time required for the animals to leave the lateral position following the application of the electrical shock. The compound failed to protect the animals from death from electrical shock, the death rate of the animals in the experimental group being 30% as compared with 33% in the controls. However, the duration of the post-shock effect in the experimental animals was 48% less ($P < 0.001$). This reduction in the duration of the post-shock effect following treatment with (I) shows it to have a significant antishock effect.

The effect of (I) on body temperature in animals was examined dynamically (after 0.5, 1, 2, 4, and 6 h following treatment) in doses of 0.05 and 0.1 g/kg. The temperature was measured with a rectal sensor for mice, using a TPEM electrical thermometer. In these doses, (I) had no effect on the body temperature of the animals.

Studies of orientational and exploratory activity were carried out using a special Animex chamber (LKB, Sweden), which enabled all types of movement of the animals to be assessed, together with changes in the position of the body in space. The period during which the orientational and exploratory activity was recorded was 5 min. The compound increased orientational and exploratory activity in mice by 74%.

The increase in orientational and exploratory activity in mice following treatment with (I) may apparently be regarded as a tranquillizing effect, since the compound showed no stimulatory activity [7, 8, 12].

These studies have shown that (I) possesses low biological activity, but the results are of interest in the general evaluation of the biological activity of organosilicon compounds.

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TESTING OF THE ACTIVITY OF WATER-SOLUBLE DERIVATIVES OF PHYTOMENADIONE IN EXPERIMENTAL HYPOCOAGULATION. II*

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The purpose of this work was to study the influence of the water-soluble tetrasodium salt of dihydrovitamin K_1 diphosphate (2-methyl-3-phytyl-1,4-diphosphate of naphthohydroquinone) on the ability of the blood of animals to clot under conditions of experimental hypocoagulation.

The tetrasodium salt of dihydrovitamin K_1 diphosphate (I) was produced at the Chair of Chemistry and Technology of Fine Organic Compounds of M. V. Lomonosov Moscow Institute of Fine Chemical Technology on the basis of dihydrovitamin K and represents a white powdered substance, readily soluble in water and virtually insoluble in alcohol and ether. The UV spectrum of I has a characteristic absorption maximum at the wavelength 237 nm ($E_{1\%}^{1\%}{}_{cm}$ 860), while a singlet signal with chemical shift δ 1.2 ppm in comparison with the position of the signal of 85% orthophosphoric acid, taken as the zero, is noted in the ^{31}P NMR spectrum.†

*For Communication I, see [1].

†The UV spectrum was recorded in methanol on a Specord UV-vis instrument (USA). The ^{31}P NMR

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