LITERATURE CITED

1. Ya. V. Dobrynin, T. G. Nikolaeva, V. I. Mukhanov, et al., Khim.-farm. Zh., No. 5, 33-38 (1978).
2. Z. P. Sof'ina, G. N. Platonova, N. A. Lesnaya, et al., Khim.-farm. Zh., No. 6, 93-95 (1978).
3. V. I. Mukhanov, I. V. Yartseva, L. V. Éktova, et al., Khim. Geterotsikl. Soedin., No. 2, 224-229 (1979).
4. A. P. Terent'ev, M. N. Preobrazhenskaya, A. S. Bobkov, et al., Zh. Obshch. Khim., 29, No. 8, 2541-2551 (1959).

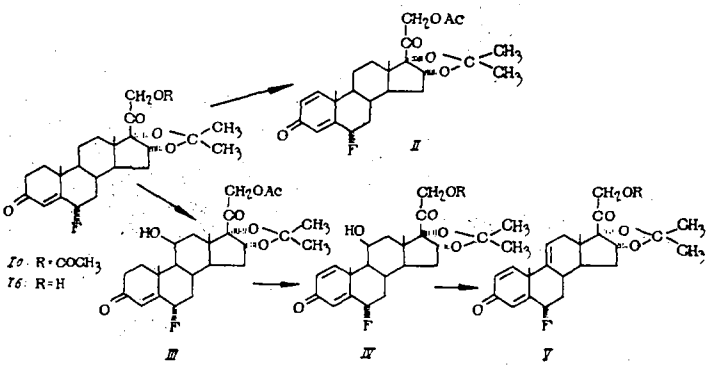
FLUOROSTEROIDS.

VII. SYNTHESIS AND BIOLOGICAL ACTIVITY OF DERIVATIVES OF 6α-FLUORO-16α,17α-ISOPROPYLIDENEDIHYDROXYPREGNA-1,4-DIENE-11β,21-DIOL-3,20-DIONE

V. M. Ryzhkova, T. I. Gusarova, G. S. Grinenko, M. L. Gerasimova, T. M. Bykova, G. A. Klubnichkina, A. I. Terekhina, G. I. Gritsina, O. N. Kruglova, and L. A. Antipova

UDC 546.16:546.07

In order to select the best method for the synthesis of 6α-fluoro-16α,17α-isopropylidenedihydroxypregna-1,4-diene-11β,21-diol-3,20-dione 21-acetate (IV), which is used as a medicinal [1] and as an intermediate in the synthesis of the more effective 9,11-halo-substituted compounds [2], we have investigated several routes for the introduction of the Δ^1-double bond and the 11β-oxygen function into the 6α-fluoro-16α,17α-isopropylidenedihydroxypregn-4-en-21-ol-3,20-dione (Ib) molecule.



We reported in a previous paper [3] that the best results in the 11β-hydroxylation of (I) were obtained using a Soviet strain of *Tieghemella orchidis*.

The next step was to find a method of introducing the Δ^1-double bond into the steroid molecule. Both microbiological and chemical methods of dehydrogenation at different stages of the synthesis were examined.

Methyl selenite was used as a dehydrogenating agent [4]. However, the diene (II) failed to undergo conversion either with an 11β-hydroxylating strain of *T. orchidis*, or with an 11α-hydroxylating strain of *Trichothecium roseum* [5]. In order to make sure that no inhibiting factors (organoselenium impurities) were present when the chemical method for the preparation of the diene (II) was employed, the latter was obtained microbiologically using the dehydrogenating microorganism *Corynebacterium simplex*, in 80% yield. Attempts to hydroxylate the diene (II) obtained in this way were similarly unsuccessful: A culture of *Tr. roseum* was virtually without effect on the steroid, and the *T. orchidis* culture gave no more than 15%

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Scientific-Research Institute for the Biological Testing of Chemical Compounds, Moscow Province. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 3, pp. 317-322, March, 1982. Original article submitted June 30, 1981.

 0091-150X/82/1603-0216$07.50

TABLE 1. Effect of a C-11 Hydroxyl Group on the Rate of Dehydrogenation of Hydroxysteroids by a Culture of *Corynebacterium simplex*

Substrate	Fermentation time, h	
	6	24
	amount of unreacted steroid, %	
6α-Fluoro-16α, 17α-isopropylidenedihydroxy-4-en-11 α,21-diol-3,20-dione (Ib)	10	Traces
6α-Fluoro-16α,17α-isopropylidenedihydroxypregn-4-en-11β,	27	"
6α-Fluoro-16α,17α-isopropylidenedihydroxypregn-4-en-21-ol-3,20-dione	37	"

of the 11β-hydroxylated compound.

1,2-Dehydrogenation of the hydroxylated steroids (III) by fermentation gave the results shown in Table 1. It will be seen from this that the presence of a hydroxyl group at C-11 reduces the rate of dehydrogenation by 20-30%, which does not substantially affect the satisfactory course of the reaction.

The microbiological introduction of the double bond into the 11β-hydroxy-compound (III) was carried out on a large scale. The yield of the Δ^1-derivative (IV) was 80%.

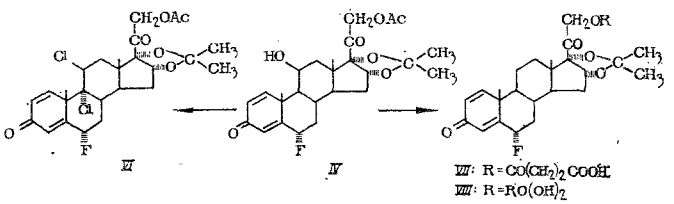
The structures of the Δ^1-compounds obtained were confirmed by the presence in the PMR spectra of two signals characteristic of protons at C-1 and C-2, which appear as two doublets centered on 6.95 (C-1) and 6.22 (C-2) ppm.

The low solubility of the isopropylidenedihydroxysteroids and the consequent need to employ large volumes of solvent for extraction, together with other technical difficulties encountered when the two microbiological stages of synthesis are carried out separately, stimulated us to examine the possibility of carrying out the hydroxylation and dehydrogenation in one stage without isolation of the intermediate reaction product [6]. The reaction sequence adopted was such that the 11β-hydroxylation preceded the dehydrogenation [7].

The direct elimination of the 11β-hydroxy group to give the $\Delta^{9,11}$ double bond was effected by reaction with thionyl chloride in pyridine. The yield of the $\Delta^{1,4,9(11)}$-triene (V) was 98% of theory. The presence of the $\Delta^{9(11)}$ double bond was confirmed by the presence in the PMR spectrum of a signal for the proton at C-11 in the form of a doublet at 5.49 ppm, with a splitting constant J of 2.5 Hz.

The conversion of (V) into the highly active difluorinated corticosteroid fluocinolone acetonide can be effected by known methods [8].

Starting from (IV), we have synthesized the 9α,11β-dichloride (VI) which possesses according to the literature [2, 9] high glucocorticoid and antiinflammatory activity.



In order to study the biological activity of the intermediate (IV), the water-soluble 21-hemisuccinate (VII) and the 21-phosphate (VIII) [10] were prepared.

Compounds (VII) and (VIII) were tested in the Laboratory for Zootechnical Endocrinology of the All-Union Institute of Animal Husbandry, VASKhNIL (V. I. Lenin Order of Lenin Academy of Agricultural Sciences). The ability of these compounds to cause premature parturition and to shorten the fetal bearing period in karakul sheep in order to obtain Persian lambskins was examined. It was found that in conjunction with an estrogen, (VII) substantially increased

TABLE 2. Glucocorticoid, Thymolytic, and Antiinflammatory Activity of the Compounds by 4-Day Subcutaneous Administration to Adrenalectomized Rats, in a Daily Dose of 0.5 mg/kg

Compound	Weight of animals, g		Liver glycogen content, g		Plasma sugar level, mg		Weight of thymus, mg per 100 g body weight		Weight of dry inflammatory granuloma, mg	
	initial	final	$M \pm m$	P	$M \pm m$	P	$M \pm m$	P	$M \pm m$	P
DOCSA	149	145	0,8±0,05	—	73,7±2,1	—	404,1±19,4	—	21,0±1,7	—
Dexamethasone	148	118	2,9±0,5	<0,001	110,8±5,4	<0,001	93,8±3,7	<0,01	12,2±1,2	<0,001
IV	148	120	3,2±0,4	<0,001	104,0±9,7	<0,01	76,0±5,1	<0,001	12,1±1,2	<0,002
V	148	139	1,5±0,1	<0,001	65,5±3,7	<0,05	313,7±2,7	<0,01	18,7±1,2	>0,05
VI	148	127	2,9±0,4	<0,001	87,0±2,7	<0,002	85,9±3,7	<0,001	13,1±0,7	<0,001

Note: Eight animals per group.

TABLE 3. Effect of the Compounds on the Urinary Excretion of Sodium and Potassium Ions (in mg per 3 h) Following a Single Subcutaneous Dose of 2 mg/kg (M ± m) to Adrenalectomized Rats

Compound	Number of animals	Na	K	Na/K
Dexamethasone	20	3,0±0,4	1,7±0,2	2,0±0,3
DOCSA	22	0,9±0,1*	3,3±0,3*	0,3±0,03*
IV	9	1,3±0,3*	2,1±0,3	0,7±0,1*
V	10	3,3±0,5*	3,5±0,3*	1,6±0,2
VI	8	4,2±0,4*	5,8±0,4*	0,7±0,06*

*Significantly different from controls.

stimulation of parturition (80% as compared with 50%), whereas at the dose level tested (VIII) displayed no such activity [11].

The androgenic, anabolic, gestagenic, uterotropic, antiandrogenic, antiestrogenic, thymolytic, antiinflammatory, glucocorticoid, and mineralocorticoid activities of compounds (IV-VI) were examined. The methods of evaluating these types of activity have been described previously [12, 13].

The glucocorticoid, thymolytic, and antiinflammatory activity of (IV-VI) were determined in adrenalectomized male rats. The experimental results are shown in Table 2. The compounds were administered subcutaneously as an oily solution in a daily dose of 0.5 mg/kg, for four days. Examinations were carried out 24 h following the last injection of the compound. It will be seen from Table 2 that (IV) and (VI) display high glucocorticoid, thymolytic, and antiinflammatory effects. Both compounds increase the liver glycogen content 3- or 4-fold, and reduce the thymus weight by 80% and the weight of the dry inflammatory granuloma by 40%. Compound (IV) increases the sugar plasma level by approximately 40%, and (VI) by 20%. Neither compound differs in its activity from dexamethasone. Compound (V) shows a slight glucocorticoid and thymolytic effect, increasing the liver glycogen approximately twofold, and reducing the weight of the thymus by 20%. This compound has no antiinflammatory activity, and did not affect the plasma sugar level.

The results of a study of the effects of the compounds on the urinary excretion of sodium and potassium ions are shown in Table 3. It will be seen that a single dose of 2 mg/kg of (IV) to adrenalectomized rats gave a sodium-retaining effect, reducing the excretion of sodium by approximately 50%. The sodium-retaining activity of the compound was less than that of desoxycorticosterone acetate (DOCSA). Compounds (V) and (VI) increased the excretion of sodium by 70 and 40%, and increased the liberation of potassium approximately threefold.

Examination of the gestagenic activity of the compounds showed that (VI) is highly gestagenic, being more active than progesterone, its threshold effective dose being 0.008 mg/kg as compared with 0.4 mg/kg for progesterone. In a dose of 0.4 mg/kg, (IV) had a gestagenic effect equal to that of progesterone. Weak gestagenic activity was found in (V), its threshold dose being 4 mg/kg.

It has also been found that (IV) and (VI) are weakly antianabolic. In a dose of 20 mg/kg, these compounds suppress the anabolic activity of simultaneously administered testosterone propionate (2 mg/kg) by approximately 30%. Compound (IV) also showed moderate antiandrogenic activity, reducing by approximately 40% the increase in mass of the seminal vesicles and ventral prostate, stimulated by testosterone, in infantile orchidectomized rats.

Compound (VI) had antiestrogenic activity. Administration in a dose of 1 mg/kg for three days to mice reduced by approximately 50% the increase in mass of the uterus induced by estrone (10 μg/kg).

It has thus been found that (IV) and (VI) possess high antiinflammatory, glucocorticoid, and thymolytic activity, but not greater than that of dexamethasone; (IV) also displays considerable gestagenic, sodium-retaining, antianabolic, and antiandrogenic activity, whereas (VI) was highly gestagenic, and showed considerable natri- and kaliuretic, antianabolic, and antiestrogenic activity. Compound (V) displayed considerable natri- and kaliuretic activity, together with weak glucocorticoid, thymolytic, and gestagenic activity.

These results enable the following conclusions to be drawn. In the compounds examined, the nature of the substituent at the 21-position of the steroid molecule (hemisuccinate or acetate) and at the 11-position (hydroxy or chloro) had no effect on the level of antiinflammatory, glucocorticoid, or thymolytic activity [compare (IV) and (VI)]. The effects of the compounds on mineral metabolism differ depending on the substituents at the 11- and 21-positions; the 11-hydroxy 21-succinate (IV) possesses sodium-retaining activity. Compounds containing an acetate group in the 21-position, and either chlorine or no substituent in the 11-position (V), are highly natri- and kaliuretic. The level of gestagenic activity is dependent on the nature and the presence of a substituent in the 11-position of the steroid molecule, compound (VI), which possesses a chlorine atom in this position, being the most active, (IV), which has a hydroxy group, is less active, and (V), which has no substituent in this position, is of low activity.

EXPERIMENTAL

Specific rotations were measured in chloroform (1% concentration, temperature 20°C). To obtain the IR spectra, suspensions of the compounds were prepared in vaseline oil. PMR spectra were obtained on a Varian XL-10-A-12 (Switzerland) in solution in $CDCl_3$. Quantitative analysis of the culture fluids was carried out spectrophotometrically (using an SF-16 spectrophotometer). UV spectra were obtained in methanol solution.

6α-Fluoro-16α,17α-isopropylidenehydroxypregna-1,4-diene-21-ol-3,20-dione 21-Acetate (II). In a flask fitted with a stirrer, a Dean–Stark apparatus, and a dropping funnel, was placed 150 ml of butyl acetate, and the solvent was heated and distilled, moisture being removed in the fraction bp 110-115°C (in the vapor). The liquid was cooled to 30-35°C, and 15 g of (Ia) added. The mixture was again heated to boiling, and a solution of methyl selenite was added slowly in a stream of inert gas, the water formed in the reaction being simultaneously distilled off. The methyl selenite was obtained by dissolving 8.4 g of selenious acid in 13.8 ml of dry methanol with the addition of 9.6 ml of glacial acetic acid. Before adding it to the reaction mixture, the reaction mixture was diluted with an equal volume of dry butyl acetate. When all the methyl selenite had been added, boiling was continued, the reaction being followed by TLC. When the concentration of starting material fell to 5%, the reaction was terminated. The solution was filtered to remove metallic selenium, and the filtrate was treated with 38 ml of 30% hydrogen peroxide and stirred for 3 h at room temperature. The colorless solution was transferred to a separatory funnel, and washed with water until neutral, 15% sodium sulfite until the aqueous layer was no longer colored, followed by water until again neutral. The extract was dried, and the solvent distilled off *in vacuo*. The residue was triturated with ether and filtered to give 9.85 g (65.7%) of the $\Delta^{1,4}$-diene 21-acetate (II), mp 257.5-258°C. $[\alpha]_D^{20}$ +76.1° (1%, $CHCl_3$).

Preparation of 6α-Fluoro-16α,17α-isopropylidenedihydroxypregna-1,4-diene-21-ol-3,20-dione (II) Using *Corynebacterium simplex*. The culture of *C. simplex* was grown in flasks on a shaker (220 rpm) at 26-28°C on a medium with the composition: peptone 6 g, enzymic hydrolysate of casein, 4g, autolyzed yeast 3 g, meat-peptone broth 150 ml, glucose 1 g, tap water 1000 ml, pH 6.7-6.8.

After one day's growth, the contents of eight flasks (800 ml) were transferred to 7 liters of a medium of the composition: autolyzed yeast 2 g, monopotassium phosphate 1 g, disodium phosphate 4.5 g, and tap water 1000 ml.

The culture was grown in a laboratory fermenter with a driven stirrer (700 rpm), air being fed in at 0.5 liter/liter/min. The substrate (I) (3.5 g) was dissolved in 170 ml of DMF and added in portions to the fermenter. The first portion of the steroid solution was added after five hours' growth (40 ml), followed after 4 h by 60 ml, and after a further 4 h, 70 ml of the solution. The course of the reaction was followed by chromatography on Silufol UV-254 plates in the system methylene chloride–methanol–water (19:1:0.1). The duration of the fermentation was 20 h. When the reaction was complete, the culture fluid was acidified with 10% sulfuric acid to pH 3.0, and extracted with ethyl acetate. The extract was washed with water, dried, and the solvent removed *in vacuo*. The residue was dissolved in 15 ml of glacial acetic acid, 2.1 g of barium acetate added, and kept for 20 h at room temperature. The reaction mixture was then poured into 150 ml of water, and the precipitate was filtered off, washed with water, and dried to give 3.35 g (80%) of (II), similar to the sample obtained by the chemical dehydrogenation of (Ia).

The dehydrogenation of the steroidal substrates (I) and (II), in order to demonstrate the dependence of the rate of transformation on the structure of the steroid molecule, was carried out in flasks on a medium of the above composition, the steroid being introduced in 30 mg amounts in 2 ml of DMF per 100 ml of medium.

6α-Fluoro-16α,17α-isopropylidenedihydroxypregna-1,4-diene-11β,21-diol-3,20)dione 21-Acetate (IVa). Compound (IIIb) (42 g) was subjected to transformation by *Corynebacterium simplex* as described above. After extraction of the culture fluid and evaporation of the solvent, the residue was dissolved in 400 ml of glacial acetic acid, and 15.2 ml of acetic anhydride and 19 g of barium acetate were then added. After 24 h, the reaction mixture was poured into 2.5 liters of water, and the precipitate filtered off and washed with water to give 36 g of (IVa), mp 270-271°C (from methylene chloride–methanol), $[\alpha]_D$ +92.36°. According to the literature [14], mp 278-281°C, $[\alpha]_D$ +92°.

6α-Fluoro-16α,17α-isopropylidenedihydroxypregn-1,4,9(11)-triene-21-ol-3,20-dione 21-Acetate (V). To a suspension of 4 g of the diene 21-acetate (IVa) in 25 ml of pyridine was added at 0°C 0.6 ml of thionyl chloride. The temperature of the reaction mixture rose to 5°C, and the solid dissolved. Completion of the reaction was determined by TLC (hexane–acetone, 9:1), from the absence of a spot from the starting material. To the reaction solution, cooled to 0°C, was added 100 ml of a 5% solution of hydrochloric acid. The precipitate which separated was filtered off, washed with 5% hydrochloric acid and water to give 3.76 g (97%) of the triene (V), mp 238-238.5°C, $[\alpha]_D^{20}$ +30°. According to the literature [15], mp 241-242.5°C, $[\alpha]_D^{20}$ +30°.

6α-Fluoro-9α,11α-dichloro-16α,17α-isopropylidenedihydroxypregn-1,4-diene-21-ol-3,20-dione 21-Acetate (VI). To a solution of 1.2 g of (IV) in 35 ml of methylene chloride containing 0.4 ml of pyridine was added gradually a mixture of 0.36 ml of thionyl chloride in 25 ml of carbon tetrachloride and 3 ml of a 10% solution of gaseous chlorine in CCl_4. The reaction mixture was stirred for 15 min, then transferred to a separatory funnel and the organic layer washed with dilute hydrochloric acid, followed by water until neutral. The solvent was removed *in vacuo*, and the residue recrystallized from a mixture of acetone and hexane to give 0.78 g of (V), mp 243.5°C, $[\alpha]_D$ +118°. PMR spectrum, δ, ppm: 1.00 (18–CH_3); 1.47 (19–CH_3); 1.18 and 1.74 [=$C(CH_3)_2$]; 2.2 (–OOCH_3); 4.67 (11–H); 4.78 (–CH_2–); 5.03 (16–H); 5.13 and 5.63 (6–H); 6.39 (4–H); 6.47 (2–H); 7.11 (1–H). Literature mp [2], 244-245°C.

6α-Fluoro-16α,17α-isopropylidenedihydroxypregna-1,4-diene-11β-ol-3,20-dione 21-Hemisuccinate (VII). To a solution of 4 g of (IVb) in 50 ml of dry pyridine was added 2.85 g of succinic anhydride, and the reaction mixture was kept for 24 h at room temperature. When the reaction was complete, the solution was poured into a mixture of 0.5 liter of 2% hydrochloric acid and ice. The precipitate which separated was filtered off, washed with water, and dried to give 3.75 g of (VII), mp 196.5°C (from a mixture of methylene chloride and hexane), $[\alpha]_D^{20}$ +92.08°. Found, %: C 63.14; H 6.07. $C_{28}H_{35}FO_9$. Calculated, %: C 63.15; H 6.25. IR spectrum, ν, cm^{-1}: 3400, 2700-2500, 1755-1730, 1660, 1630. UV spectrum, λ_{max}, nm: (log ε) 242-244 (4.19).

6α-Fluoro-16α,17α-isopropylidenedihydroxypregna-1,4-diene-11β-ol-3,20-dione 21-Phosphate (VIII). To a solution of 3.6 g of (IVb) in 50 ml of dry tetrahydrofuran (THF), cooled to –40°C, was added slowly 5 g (3.5 ml) of freshly prepared pyrophosphoryl chloride in 10 ml of THF. The reaction mixture was kept for 4 h at –40°C, and 150 ml of water was then added. The THF was distilled off *in vacuo*, and the solid which separated was filtered off to give 1.2 g of (VIII), mp 232.5°C, $[\alpha]_D^{20}$ +89.7°.

LITERATURE CITED

1. US Patent No. 3,014,938 (1964); Chem. Abstr., 56, No. 10242c.
2. Danish Patent No. 124,678; Ref. Zh. Khim., No. 14N471P (1974).
3. V. M. Ryzhkova, T. I. Gusarova, G. A. Klubnichkina, et al., Khim.-farm. Zh., No. 12, 69 (1980).
4. Z. A. Pryakhina and V. I. Maksimov, Author's Certificate No. 306,120 (USSR); Otkrytiya, No. 19, 83 (1971).
5. US Patent No. 3,079,384; Chem. Abstr., 59, No. 2911 (1963).
6. French Patent No. 2,000,716; Chem. Abstr., 72, No. 88919 (1970).
7. V. M. Ryzhkova, G. A. Klubnichkina, A. A. Shpingis, et al., Author's Certificate No. 571,489 (USSR); Otkrytiya, No. 33, 69 (1977).
8. G. S. Grinenko, V. I. Bayunova, R. G. Karpenko, et al., Khim.-farm. Zh., No. 7, 110 (1978).

9. H. Reimann, E. P. Oliveto, R. Neri, et al., J. Am. Chem. Soc., 82, 2308 (1960).
10. G. S. Grinenko, V. M. Ryzhkova, N. P. Sorokina, et al., Author's Certificate No. 555,115 (USSR); Otkrytiya, No. 15, 73 (1977).
11. A. L. Laducheva and B. Zh. Yakubov, Ovtsevodstvo, No. 3, 29 (1977).
12. A. I. Terekhina, Z. I. Istomina, A. V. Kamernitskii, et al., Khim.-farm. Zh., No. 10, 17 (1975).
13. T. I. Gusarova, G. S. Grinenko, A. I. Terekhina, et al., Khim.-farm. Zh., No. 5, 34-37 (1976).
14. W. S. Allen, S. Bernstein, L. I. Feldman, et al., J. Am. Chem. Soc., 82, 3696 (1960).
15. M. Heller, R. H. Lenhard, and S. Bernstein, Steroids, 7, 381 (1966).

HEMOSTATIC ACTIVITY OF THE POLYMER FERAKRIL

V. Z. Annenkova, A. T. Platonova,* G. M. Kononchuk, N. G. Dianova, V. B. Kazimirovskaya, V. M. Annenkova, G. S. Ugryumova, and M. G. Voronkov

UDC 615.273.53:678.744.322].036.8

We have previously reported [1, 2] the synthesis of the water-soluble polymer Ferakril. This communication gives the results of a study of the hemostatic activity of this polymer, which is an iron-containing polyacrylic acid.

EXPERIMENTAL

The hemostatic activity of Ferakril was determined using standard methods [3]. Measurement of the LD_{50} by Kerber's method [4] in white mice weighing 18-20 g showed it to be greater than 3000 mg/kg, so that Ferakril may be regarded as a relatively harmless compound. Statistical treatment of the results was carried out by the difference method [5]. M, m, T, and n in the tables represent respectively the mean arithmetical value of the measured parameter, the arithmetical error, Student's criterion, and the number of variants. The suffices c and e denote control and experimental. The reliability of the differences was determined by Student's criterion. For a threshold probability of 0.95 and number of degrees of freedom $f = 10 - 1 = 9$, the differences were regarded as significant when $T > T_{05} = 2.262$.

The coagulatory activity of Ferakril was studied *in vitro* in the blood from donors and various animals. Addition of a solution of Ferakril (in isotonic sodium chloride solution) to stabilized blood caused the proteins to coagulate with the formation of a clot. To obtain a volumetrically and mechanically stable clot, it was necessary to add 5-10 mg of Ferakril per 1 ml of blood plasma.

To determine the effects of blood coagulation factors on the coagulatory activity of the polymer, the Ferakril solution was added to heparinized blood, an erythrocyte mass, blood serum, and solutions of fibrinogen and albumin. In all cases, at a certain ratio of protein

*Deceased.

TABLE 1. Effect of the Concentration of Ferakril on Its Hemostatic Effects†

Statistical factor	Concentration of solutions, %						
	0*	0,25	0,5	1,0	2,0	5,0	10,0
M	1100	1087	850	84	66	100	836
$\pm m$	42,6	51,8	78,6	3,0	3,6	8,3	61,2
T	—	0,19	2,79	23,5	24,2	23,0	3,51
n	10	10	10	10	10	10	10

*Isotonic sodium chloride solution.
†Dimensions of wound, 2 × 2 × 50 mm.

Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Irkutsk. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 3, pp. 322-325, March, 1982. Original article submitted May 28, 1981.

 0091-150X/82/1603-0222$07.50