IMIDAZOLES.

XVI. SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 1-BENZYL-4-NITROIMIDAZOLE-5-THIOACETIC ACIDS

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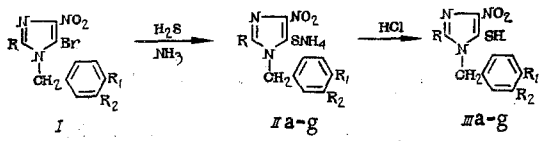
It was established in the 1960's that 4,5-aminoimidazolecarboxamides are involved in nucleic acid metabolism, and possess slight antiblastic activity against leukemia strain L-1210. This provided a stimulus for a search for new imidazoles with potential antitumor activity [1-4]. The imidazole nucleus was used to introduce a variety of alkylating groups, including the bischloroethylamino group [5, 6]. These investigations resulted in the introduction of drugs into oncological practice [7, 8].

Several imidazoles are also known to possess high protisticidal activity [9].

With a view to studying their antitumor and protisticidal properties, the synthesis was therefore undertaken of some amides and nitriles of 1-benzyl-4-nitroimidazole-5-thioacetic acids. The results are presented in this communication.

The starting materials used were 2-substituted -1-benzyl-4-nitro-5-bromo imidazoles (I), obtained by brominating the corresponding 1-benzyl-4-nitroimidazoles [10]. Similarly obtained were the 4-methoxy-3-nitrobenzyl derivatives of I ($R = CH_3$, $R_1 = CH_3O$, $R_2 = NO_2$).

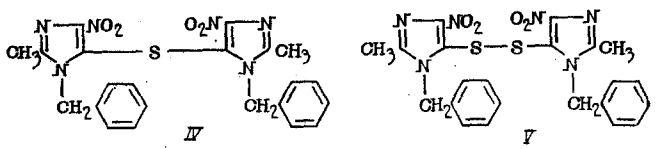
The bromine atom in I was replaced by mercapto by treatment with hydrogen sulfide in ethanolic ammonia.



I II a-g III a-g

R=H, CH_3; R_1=H, F, Cl, CH_3O; R_2=H, NO_2.

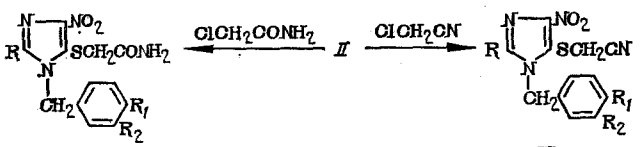
Under the conditions in which the ammonium salts II were prepared, there was the possibility of the formation of diimidazole sulfides and disulfides. Reaction of the 5-bromine-substituted imidazole I ($R = CH_3$, $R_1 = R_2 = H$) with the ammonium salt IId in ethanol afforded the diimidazolyl sulfide, IV.



IV V

The diimidazolyl disulfide, V, was prepared by oxidizing the mercaptoimidazole IIId with potassium ferricyanide in alkaline solution.

The amides and nitriles of the imidazole-5-thioacetic acids (VI and VII) were synthesized by reacting the ammonium salts II with chloroacetamide or chloroacetonitrile.



VI a-f VII a-e

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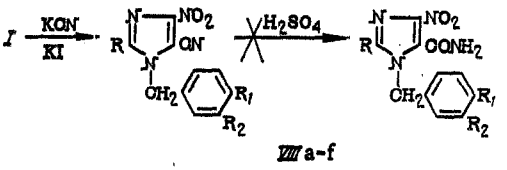
TABLE 1. Biological Activity of VI(a–d) and VII(b–e)

Compound	Toxicity to mice‡ mg kg			Antitumor activity									Protisticidal activity*	
				rats					mice					
					sarcoma 45		Walker's carcinosarcoma 256			sarcoma 180		Ehrlich's ascites	entamebae	balantidae
	LD_{100}	LD_{50}	MTD††	dose, mg/kg	R**, %	α	R**, %	α	dose, mg/kg	R**, %	α	MDL†, %	dose, mg/kg	
VIa	1250	—	1000	100	35	0,95	0	—	200	0	—	0	1,0	1,0
VIb	1500	1275 (1099–1479)	1000	100	0		0	—	200	0	—	0	1,0	1,0
VIc	1500	1240 (1060–1450)	1000	100	35	0,95	37	0,95	200	0	—	123	0,1	0,1
VId	1500	1220 (1034–1439)	1000	100	0	—	36	0,95	200	0	—	128	0,1	0,1
VIe	1500	1200 (1008–1428)	1000	100	0	—	0	—	200	0	—	0	0,01	0,1
VIf	>3500			200	75	>0,98	39	0,95	400	0	—	0	1,0	1,0
VIIb	1500	1220 (1043–1427)	900	80	34	0,95	0	—	150	0	—	0	0,01	0,1
VIIc	1250	780 (639–951)	500	50	0	—	0	—	100	0	—	0	0,1	1,0
VIId	1500	1050 (905–1218)	750	80	53	>0,95	43	>0,95	150	30	0,95	132	0,01	0,1
VIIe	>3500			200	57	>0,95	30	0,95	400	37	0,95	0	0,1	1,0

Notes. *As a measure of their protisticidal activity, the minimum concentration of the drug which retarded the growth of cultures after 24, 48, and 72 h is given. †The MDL is the mean duration of life (controls taken as 100%). ‡In determining the toxicities, each dose was tested in four mice, but in the chemotherapeutic experiments each group consisted of eight animals. **R is the retardation of tumor growth. ††The MTD is the maximum tolerated dose. Range given in parentheses.

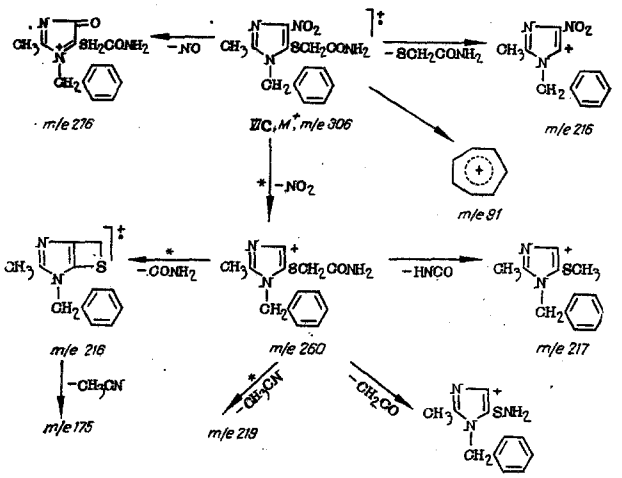
The bromine atom in I was also replaced by the cyano-group, by treatment with potassium cyanide in the presence of potassium iodide.



VIII a-f

It was, however, not possible to isolate the corresponding imidazole-5-carboxamides by hydrolyzing VIII in sulfuric acid.

Further proof of the structures of VI, VII, and VIII was obtained from their mass spectra. Breakdown of the molecular ion of the thioacetamide VIc under electron impact occurred with the initial elimination of nitroso- and nitro-groups. Further dissociative ionization of VIc was due to breakdown of the carboxamide group or elimination of CH_3CN from the ions $(M-NO)^+$ and $(M-NO_2)^+$.



Ions with masses 217 and 218 result from rearrangement; their formation from carboxamides having been described in the literature [11, 12]. Breakdown of the $(M-NO)^+$ ion of m/e 276 proceeds similarly to the breakdown of $(M-NO_2)^+$, and is not shown in the diagram.

When halogen is introduced into the benzyl substituent of VI (VId and VIe), the intensity of the ion of mass $(M-NO_2)^+$ decreases, and the $(M-NO)^+$ ion is virtually absent from the spectra.

In the mass spectra of the thioacetonitriles VIIb and VIId, the molecular ion peak is present together with a fragment of mass $(M-SCH_2CN)^+$ and the corresponding tropylium cation. Unlike the thioacetamides (VI), no fission of the NO or NO_2 groups is observed in the spectra of VII.

The mass spectrum of 1-benzyl-2-methyl-4-nitro-5-cyanoimidazole (VIIIc) contains peaks due to the molecular ion, $(M-NO)^+$, and the tropylium cation. In the spectrum of the chloroderivative of this series (VIIIe), as in the cases of VId and VIe, no peak due to the $(M-NO)^+$ ion was present.

The course of the fragmentation of VI, VII, and VIII is probably due to ejection of the tropylium cation competing with the elimination of NO and NO_2. In favor of this interpretation is the increase in the intensity (relative to the total ion current) of the tropylium peak in the mass spectra of the thioacetamides, as follows: VIc — 26.3%; VIe — 43.2%; and VId — 56.8%.

EXPERIMENTAL PHARMACOLOGICAL

The chemotherapeutic experiments carried out to study the antiblastic properties utilized well-known procedures [13, 14].

Toxicities were determined in mongrel white mice following a single intraperitoneal dose, and antitumor activities were determined in rats and mice with a variety of transplanted tumors (sarcoma 45, Walker's carcinosarcoma 256, sarcoma 180, and Ehrlich's ascitic carcinoma). In all, 400 mice and 200 rats were used.

Protisticidal activity was assessed in four strains of intestinal bacteria (*Entamoeba histolytica, Entamoeba moshkovskii, Balantidium coli, Balantidium suis*), by methods described in the literature [15, 16]. The compounds were tested in a wide range of doses (1.0, 0.1, 0.01, 0.002 and 0.001 mg/ml).

The toxicities of VI and VII were found to be virtually identical (LD_{100} = 1250-1500 mg/kg). Introduction of the 4-methoxy-3-nitrobenzyl radical reduced the toxicity of the corresponding thioacetamide (VIf) and nitrile (VIIe) substantially (LD_{100} > 3500 mg/kg) (Table 1).

A study of the antiblastic properties of these compounds showed that most of them were weakly active against the rat tumors used (they inhibited tumor growth by 30-50%), except for the 4-methoxy-3-nitrobenzylthioacetamide, VIf, which inhibited the growth of sarcoma 45 by more than 70%. In mouse tumors, however, these compounds in general showed no suppressive effects (Table 1).

The results of a study of the protisticidal activity of VI and VII showed that at a dose of 1 mg/ml they were lethal to the protozoal strains. Compounds VId, VIe, VIIb, and VIId, in concentrations of 0.1 mg/ml, suppressed to a similar extent the growth of the amoebae and Balantidae. The most active compounds were the benzyl (VIIb) and the 4-chlorobenzyl (VIe and VIId) derivatives, which were totally protisticidal against the amoebae in a dilution of 0.01 mg/ml (Table 1).

The 4-nitro-5-cyanoimidazoles VIII exhibited protisticidal properties for the most part at a concentration of 1 mg/ml. The most active compound of this series, VIIIf, retarded the growth of the Protozoa in a dilution of 0.1 mg/ml. Unlike VIc and VIIb, 1-benzyl-2-methyl-4-nitro-5-cyanoimidazole (VIIIc) was inactive.

Practically speaking, the most active compounds, in terms of their protisticidal activity, were 50-100 times less active than the well-known drugs emetine and metronidazole.

Examination of the biological results reveals some parallelism between antiblastic and protisticidal activity.

EXPERIMENTAL CHEMICAL

Mass spectra were recorded on an MX-1303 spectrometer with direct introduction of the sample into the ion source at a temperature 30-40° below the mp of the material.

Chromatography was carried out on Silufol UV-254 plates, using the solvent systems acetone–hexane (3:2) for the mercapto (III) and acetamido (VI) derivatives, and acetone–hexane (1:1) for the cyano-derivatives VII and VIII. Visualization was by UV.

1-(4-Methoxy-3-nitrobenzyl)-2-methyl-4-nitroimidazole was obtained from 16.5 g (0.1 mole) of the potassium salt of 2-methyl-4(5)-nitroimidazole, 50 ml of DMF, and 16.6 g (0.1 mole) of 4-methoxy-3-nitrobenzyl chloride [10]. Yield 21.5 g (73.5%), mp 150-152°C (from ethanol). Found, %: C 49.17; H 3.90; N 19.12. $C_{12}H_{12}N_4O_5$. Calculated, %: C 49.31; H 4.13; N 19.17.

1-(4-Methoxy-3-nitrobenzyl)-2-methyl-4-nitro-5-bromoimidazole (I) was obtained from 14.6 g (0.05 mole) of 1-(4-methoxy-3-nitrobenzyl)-2-methyl-4-nitroimidazole, 40 ml of DMA, and 3.1 ml (0.06 mole) of bromine [10]. The yield of I was 14.0 g (75.4%), mp 162-164°C (from ethanol). Found, %: Br 21.30; N 14.90. $C_{12}H_{11}BrN_4O_5$. Calculated, %: Br 21.52; N 15.09.

Ammonium Salts of 1,2-Substituted 4-Nitro-5-mercaptoimidazoles (II). Into a mixture of 0.01 mole of I, 40 ml of ethanolic ammonia, and 8-10 ml of DMF (sufficient to completely dissolve I) was passed a stream of dry hydrogen sulfide, with stirring, for 12-15 min, and stir-

TABLE 2. Properties of Substituted 1-Benzyl-(2-methyl)-4-nitro-5-thio(cyano)imidazoles

Compound	R	R_1	R_2	R_3	Yield, %	T., °C	Found, %				Molecular formula	Calculated, %				R_f
							C	H	N	S		C	H	N	S	
IIa	H	H	H	SNH_4	54	175—17	—	—	22,14	12,56	$C_{10}H_{12}N_4O_2S$	—	—	22,21	12,71	—
IIb	H	F	H	SNH_4	55	184	—	—	20,70	11,64	$C_{10}H_{11}FN_4O_2S$	—	—	20,73	11,87	—
IIc	H	CP	H	SNH_4	56	199—200	—	—	19,24	11,10	$C_{10}H_{11}ClN_4O_2S$	—	—	19,54	11,18	—
IId	CH_3	H	H	SNH_4	61	180—18	—	—	21,30	12,00	$C_{11}H_{14}N_4O_2S$	—	—	21,04	12,04	—
IIe	CH_3	F	H	SNH_4	69	199—200	—	—	19,55	11,50	$C_{11}H_{13}FN_4O_2S$	—	—	19,71	11,28	—
IIf	CH_3	Cl	H	SNH_4	65	202—203	—	—	18,40	10,43	$C_{11}H_{13}ClN_4O_2S$	—	—	18,63	10,66	—
IIg	CH_3	CH_3O	NO_2	SNH_4	68	204—205	—	—	20,72	9,16	$C_{12}H_{15}N_5O_5S$	—	—	20,52	9,39	—
IIIa	H	H	H	SH	90	94—95	—	—	17,87	13,94	$C_{10}H_9N_3O_2S$	—	—	17,86	13,63	0,32
IIIb	H	F	H	SH	92	99—101	—	—	16,86	12,77	$C_{10}H_8FN_3O_2S$	—	—	16,59	12,66	0,36
IIIc	H	Cl	H	SH	88	105—107	—	—	15,75	12,07	$C_{10}H_8ClN_3O_2S$	—	—	15,58	11,89	0,42
IIId	CH_3	H	H	SH	93	98—100	—	—	16,65	12,57	$C_{11}H_{11}N_3O_2S$	—	—	16,86	12,86	0,42
IIIe	CH_3	F	H	SH	86	116—118	—	—	15,98	11,72	$C_{11}H_{10}FN_3O_2S$	—	—	15,72	12,00	0,52
IIIf	CH_3	Cl	H	SH	88	128—130	—	—	14,92	11,16	$C_{11}H_{10}ClN_3O_2S$	—	—	14,81	11,30	0,56
IIIg	CH_3	CH_3O	NO_2	SH	85	130—132	—	—	17,45	9,65	$C_{12}H_{12}N_4O_5S$	—	—	17,28	9,89	0,55
VIa	H	H	H	SCH_2CONH_2	60	177—178	49,51	4,19	18,93	10,66	$C_{12}H_{12}N_4O_3S$	49,30	4,14	19,17	10,97	0,53
VIb	H	Cl	H	SCH_2CONH_2	63	206—207	44,00	3,48	17,25	9,59	$C_{12}H_{11}ClN_4O_3S$	44,11	3,39	17,15	9,81	0,59
VIc	CH_3	H	H	SCH_2CONH_2	67	170—171	50,73	4,60	17,98	10,26	$C_{13}H_{14}N_4O_3S$	50,97	4,61	18,29	10,47	0,42
VId	CH_3	F	H	SCH_2CONH_2	73	199—200	48,40	3,93	17,30	10,17	$C_{13}H_{13}FN_4O_3S$	48,14	4,04	17,28	9,89	0,39
VIe	CH_3	Cl	H	SCH_2CONH_2	65	186—188	45,57	3,80	16,58	9,21	$C_{13}H_{13}ClN_4O_3S$	45,82	3,84	16,44	9,41	0,46
VIf	CH_3	CH_3O	NO_2	SCH_2CONH_2	69	194—195	44,35	4,12	18,62	8,69	$C_{14}H_{15}N_5O_6S$	44,09	3,96	18,36	8,41	0,31
VIIa	H	H	H	SCH_2CN	60	97—98	52,64	3,56	20,22	11,50	$C_{12}H_{10}N_4O_2S$	52,54	3,67	20,43	11,69	0,50
VIIb	CH_3	H	H	SCH_2CN	84	140—41	54,10	4,29	19,21	10,90	$C_{13}H_{12}N_4O_2S$	54,15	4,20	19,43	11,12	0,54
VIIc	CH_3	F	H	SCH_2CN	73	117—118	50,72	3,41	18,42	10,33	$C_{13}H_{11}FN_4O_2S$	50,97	3,62	18,25	10,47	0,53
VIId	CH_3	Cp	H	SCH_2CN	65	137—138	48,60	3,70	17,25	9,72	$C_{13}H_{11}ClN_4O_2S$	48,37	3,43	17,36	9,93	0,51
VIIe	CH_3	CH_3O	NO_2	SCH_2CN	71	162—164	46,44	3,90	19,50	8,61	$C_{14}H_{13}N_5O_5S$	46,23	3,61	19,27	8,82	0,38
VIIIa	H	H	H	CN	55	125—126	58,12	3,80	24,84	—	$C_{11}H_8N_4O_2$	57,89	3,53	24,55	—	0,80
VIIIb	H	F	H	CN	47	115—117	53,41	2,84	22,90	—	$C_{11}H_7FN_4O_2$	53,66	2,87	22,76	—	0,75
VIIIc	CH_3	H	H	CN	48	106—108	59,66	4,40	22,91	—	$C_{12}H_{10}N_4O_2$	59,50	4,16	23,13	—	0,74
VIIId	CH_3	F	H	CN	47	102—103	55,20	3,25	21,27	—	$C_{12}H_9FN_4O_2$	55,39	3,49	21,53	—	0,68
VIIIe	CH_3	Cl	H	CN	51	109—110	51,95	3,16	20,10	—	$C_{12}H_9ClN_4O_2$	52,09	3,28	20,25	—	0,58
VIIIf	CH_3	CH_3O	NO_2	CN	52	100—102	49,10	3,25	21,92	—	$C_{13}H_{11}N_5O_5$	49,21	3,50	22,08	—	0,30

Note. IIa-g and IIIa-g melted with decomposition.

ring was continued for a further 10 min. The precipitate of II which separated was filtered off and washed on the filter with acetone (Table 2).

1,2-Substituted 4-Nitro-5-mercaptoimidazoles (III). Compound II was dissolved in water with heating, and acidified with concentrated hydrochloric acid. The precipitate was filtered off (Table 2).

Di-(1-benzyl-2-methyl-4-nitroimidazol-5-yl) Sulfide (IV). A mixture of 0.5 g (0.002 mole) of IId, 0.4 g (0.002 mole) of I (R = CH_3, R_1 = R_2 = H) and 30 ml of 30% methanol was stirred at 60-70°C for 5-6 h, and kept overnight. The precipitate which separated was filtered off to give 0.6 g (53.7%), mp 198-199°C. Found, %: N 17.93; S 6.84. M 464 (by mass spectrometry). $C_{22}H_{20}N_6O_4S$. %: N 18.09; S 6.90.

Di-(1-benzyl-2-methyl-4-nitroimidazol-5-yl) Disulfide (V). To a solution of 0.1 g of potassium hydroxide in 10 ml of water was added 0.25 g (0.002 mole) of IIId, and the mixture was stirred until solution was complete. There was then added 0.35 g (0.002 mole) of potassium ferricyanide dissolved in 5 ml of water. The precipitate which separated was filtered off to give 0.2 g (80.0%) of V, mp 70-72°C. Found, %: N 17.16; S 12.78. $C_{22}H_{20}N_6O_4S_2$. Calculated, %: N 16.92; S 12.91.

Amides (VI) and Nitriles (VII) of Substituted 1-Benzyl-(2-methyl)-4-nitroimidazole-5-thioacetic Acids. A mixture of 0.01 mole of II, 0.011 mole of monochloroacetamide or monochloroacetonitrile, and 60 ml of 30-40% methanol was heated on a water bath for 6-7 h, then kept overnight. The precipitate which separated was filtered off and recrystallized from aqueous methanol (Table 2).

Mass spectrum of VIc (ion masses given, followed in parentheses by peak intensities expressed as a percentage of the main peak): 308(7) 307(14) 306(45) 276(3) 262(7) 261(15) 260(45) 234(16) 233(9) 232(9) 219(10) 218(11) 217(10) 216(24) 201(7) 200(50 175(10) 131(7) 127(15) 106(9) 91(100).

Mass spectrum of VId: 324(23) 278(24) 252(3) 237(3) 236(5) 235(4) 234(10) 109(100 91(4).

Mass spectrum of VIIe: 342(11) 340(31) 296(8) 294(25) 253(2) 252(7) 251(2) 250(8) 127(37) 125(100).

Mass spectrum of VIIb: 288(9) 217(7) 216(5) 133(12) 91(100).

Mass spectrum of VIId: 324(7) 322(18) 252(1) 250(3) 232(5) 127(43) 125(100).

Substituted 1-Benzyl-(2-methyl)-4-nitro-5-cyanomidazoles (VIII). A mixture of 0.01 mole of I, 1.3 g (0.02 mole) of potassium cyanide, 1 g of potassium iodide, and 50 ml of absolute methanol was heated on the water bath for 12-14 h, the methanol distilled off, and water added. The precipitate was filtered off and recrystallized from aqueous ethanol (Table 2).

Mass spectrum of VIIIc: 242(14) 212(5) 91(100).

Mass spectrum of VIIIe: 278(6) 276(16) 127(37) 125(100).

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THERAPEUTIC ACTIVITY OF ETHYNYL KETONES DURING EXPERIMENTAL TRICHOPHYTIA

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In preceding articles [1, 2] data were given on the biological activity of acetylenic ketones, which we synthesized. It was shown that the overwhelming majority of compounds containing the ketoethynyl fragment exhibit a pronounced fungicidal activity *in vitro*, determined by the method of double serial dilutions of the preparations in a liquid culture medium [3].

To solve the problem of the future use of ethynyl ketones as fungicidal medicinal preparations, we must verify their toxicity and therapeutic action on infected animals. For model compounds we used α-ethynyl ketones of various structures (Table 1) — diarylpropynones (compounds I, XXIV-XXXIII), acyl-substituted acetylenes (II-IV), symmetrical diacetylenic and vinyl acetylenic ketones (V-IX), acetylenic and diacetylenic ketoethers (X-XVI), δ-ketols (XVII-XVIII), hetrocyclyl-substituted mono- and diacetylenic ketones (XIX-XXIII), which are very active towards gypseum Trichophyton [ring worm] *in vitro*. The class of the compounds is fairly well represented and synthetically available. In general these compounds are prepared by the following scheme:

$$R{-}C{\equiv}CH_2 \xrightarrow[2)\ R'CHO]{1)\ MgBrEt} R{-}C{\equiv}C{-}CHOH{-}R' \xrightarrow{MnO_2} R{-}C{\equiv}C{=}CO{=}R'$$

EXPERIMENTAL

For the series of ethynyl ketones studied (I-XXIII), we determined the acute toxicity on nonpedigree white mice, by a single peroral administration of a stable aqueous emulsion of the compounds (a weighed sample of the compound was ground with 1-2 drops of a 6% Tween-80 solution and gradually diluted to the required concentration). No changes in the behavior of the mice and their state was observed after administration of the above compounds in doses of 100, 500 and 1000 mg/kg. The LD_{50}, calculated by the Pershin method [4], for all the preparations tested exceeded 1000 mg/kg.

The therapeutic effect of representatives of the series of ethynyl ketones studied was tested on a model of an experimental skin trichophytia on nonpedigree white mice (Table 1) and guinea pigs (Table 2). Each experiment was carried out on 4-10 animals. The animals were infected by a standard procedure, by rubbing a mixture of a gypseum Trichophyton culture and pathological material containing fungus elements into a preliminarily epilated and scarified section of the skin. The scarification was carried out under a surface ether narcosis. The presence of a fungal infection of skin and hair was confirmed by microscopic detection of fungal spores, and also by isolating pure cultures of pathogenic fungi during inoculation on a liquid Saburo medium with addition of antibiotics with a wide spectrum of activity (penicillin and streptomycin, 50 ED/ml in each case). The treatment of the experimental trichophytia was started 7-8 days after the appearance of definite symptoms of the disease, i.e., hyperemia, sections of baldness, scales, peeling, and a microscopic confirmation of the disease or isolation of pure cultures of gypseum Trichophyton during the inoculation of skin scrapings and hair. The focus of infection and the zone surrounding it was lubricated with Vaselin ointments containing 1-10% of the preparations tested. The prepara-

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