With respect to their anticonvulsant activity, Ia-h and IIa-h resemble the previously described [1] 5-(p-alkoxyphenyl)-5-methylhydantoins, for which anticorazole properties are also characteristic. In addition to this, IIa, b, with SI = 8.3 and 8.6 and TI = 10 and 10.5, respectively, are appreciably inferior to the most active compound IV, the SI and TI of which are 14.3 and 14.3, respectively (see Table 4). Morpholino and dimorpholino groupings evidently do not have a substantial effect on the manifestation of the anticorazole properties of hydantoins.

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SYNTHESIS OF ANALOGS OF THE ANTIBIOTIC PHERVENULIN AND ITS 4-OXIDE

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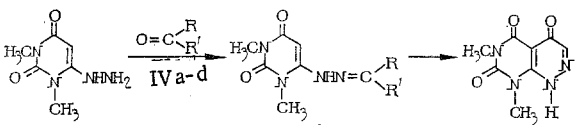
UDC 615.33(Phervenulinum)].012.1

In continuation of the search [1] for new biologically active compounds among pyrimido-as-triazines, we undertook the synthesis of analogs of the antibiotic phervenulin (I) from 1,3-dimethyl-4-hydrazino- and 1,3-dimethyl-4-hydrazino-5-nitrosouracil (II and III) [2].

By reacting (II) with carbonyl compounds (IVa-d), we have obtained the hydrazones (Va-d).



IVa-c, Va-c: R = H IVb,d- Vb,d: R' = COOH
IVd, Vd: R = CH_3 IVc, Vc: R' = $C_6H_4N(CH_2CH_2Cl)_2$-p
IVa, Va: R' = 2-nitro-5-furyl

The reaction between (II) and glyoxylic acid (IVb) proceeds in a unique fashion, since on heating in ethanol, instead of the expected hydrazone (Vb), 1,4,5,6,7,8-hexahydro-6,8-dimethylpyridazino[3,4-d]pyrimidine-4,5,7-trione (VI) was obtained. The PMR spectrum of this compound contained a singlet signal for one proton at 7.43 ppm. Signals for the NCH_3 groups of the uracil moiety were seen at 3.36 and 3.25 ppm. The IR spectrum of (VI) in the crystalline state showed absorption at 3100 cm^{-1}, showing that associated NH groups are present, but there was no absorption at 3100-3000 cm^{-1}. This same compound is apparently obtained when ethyl glyoxylate hydrazone and (II) are heated with sodium ethoxide [3].

It is noteworthy that (II) reacts with pyruvic acid (IVd) on heating in ethanol to give 1,2,3,4-tetrahydro-1,3-dimethyl-6-(methylcarboxymethylidenehydrazino)pyrimidine-2,4-dione (Vd).

We were unable to obtain the hydrazone (Vb) by reacting (II) with glyoxylic acid in ethanol at 20-25°C in the presence of hydrochloric acid.

It was shown to be possible to convert hydrazones similar to (Va-d) into the 3-substituted derivatives (I) by heating in ethanol with amyl nitrite (isoamyl nitrite) in the presence of hydrochloric acid [2]. Our attempts to carry out a similar conversion with hydrazones (Va-d) using amyl nitrite were unsuccessful.

Some derivatives of (I) were obtained from the nitrosouracil (III). Thus, reaction of (III) with the aldehyde (IV) in ethanol in the presence of hydrochloric acid afforded (VII), which is a derivative of (I).

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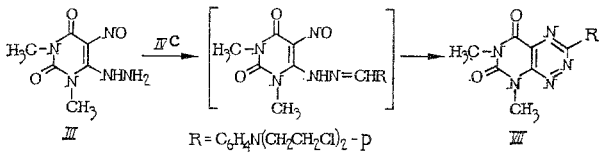
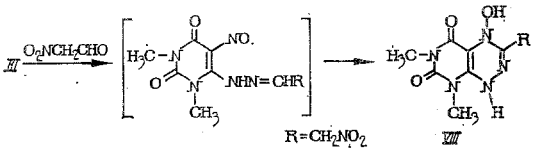
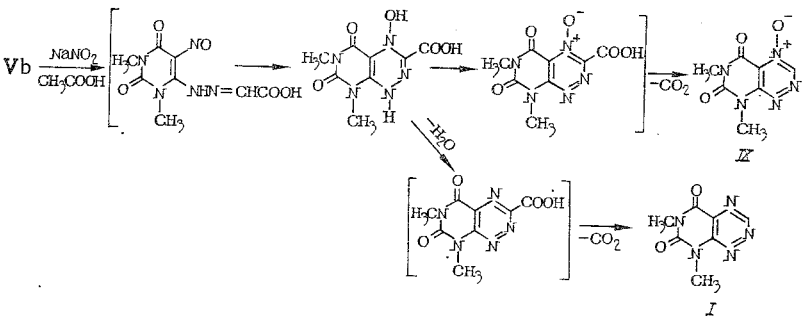


Reaction of (III) with nitroacetaldehyde gave 1,4,5,6,7,8-hexahydro-3-nitromethyl-4-hydroxy-6,8-dimethylpyrimido[5,4-e]triazine-5,7-dione (VIII). The PMR spectrum of this compound contained signals for two NCH_3 groups at 3.42 and 3.75 ppm, together with singlet signals for two equivalent protons at 6.50 ppm. The molecular mass of the compound, as determined by mass spectrometry, corresponded to the proposed structure, and the presence in the spectrum of mass $[M-17]^+$ confirmed the presence of a hydroxy group.



The nitrosation of the hydrazone (Vb) carried out here is of special interest. It was found that reaction of this compound with $NaNO_2$ in acetic acid at 20-25°C gave phervenulin 4-oxide (IX) in 45-50% yield. Furthermore, the reaction products contained some (I) (3-5%). The reaction is accompanied by considerable liberation of heat and the formation of gaseous products. The formation of (I) and its 4-oxide appears to take place as follows:



EXPERIMENTAL CHEMISTRY

The PMR spectra of the compounds were obtained in $(CD_3)_2SO$ on a Perkin-Elmer P12B instrument, working frequency 60 MHz. Chemical shifts are given on the δ scale in ppm relative to TMS.

IR spectra were recorded on a UR-20 spectrometer (East Germany). The compounds were used as pastes in vaseline oil.

The mass spectrum of (VIII) was recorded on a Varian MAT-311A instrument, accelerating voltage 3 kV, cathode emission current 300 μA, ionizing voltage 75 V, and ion temperature 200°C.

1,2,3-Tetrahydro-1,3-dimethyl-6-(5-nitrofurfuryl-2-methylidenehydrazino)pyrimidine-2,4-dione (Va), 1,2,3,4-Tetrahydro-1,3-dimethyl-6-[p-(di-2-chloroethyl)aminobenzylidenehydrazino]-pyrimidine-2,4-dione (Vc), and 1,2,3,4-Tetrahydro-1,3-dimethyl-6-(methylcarboxymethylidene-hydrazino)pyrimidine-2,4-dione (Vd) were obtained by reacting 6.0 mmole of (II) with 6.5 mmole of the appropriate carbonyl compound (IVa, b, or c) in 20 ml of ethanol at the boil for 15 min. The reaction mixture was cooled, and the precipitated (Va, c, or d) was filtered off (see Table 1).

1,2,3,4-Tetrahydro-1,3-dimethyl-6-(carboxymethylidenehydrazino)pyrimidine-2,4-dione (Vb). Compound (II) (1 g, 5.9 mmole) was dissolved in 10 ml of ethanol, 5 ml of water, and 0.5 ml of concentrated hydrochloric acid. To the resulting solution was added 0.7 g (7.6 mmole) of glyoxylic acid, and the mixture was stirred for 10 min at 20-25°C. The precipitated (Vb) was filtered off.

1,4,5,6,7,8-Hexahydro-6,8-dimethylpyridazino[3,4-d]pyrimidine-4,5,7-trione (VI). A mixture of 0.85 g (5.0 mmole) of (II) and 0.5 g (5.4 mmole) of glyoxylic acid was boiled in 20 ml of ethanol for 15-20 min, cooled, and the precipitated (VI) filtered off.

TABLE 1. Properties of Compounds (Va-d) and (VI-VIII)

Compound	mp, °C (solvent)	Yield, %	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
Va	238—9*	75—80	44,8	3,8	23,8	$C_{11}H_{11}N_5O_5$	45,0	3,8	23,9
Vb	110—2	85—90	39,9	4,8	22,5	$C_8H_{10}N_4O_4 \cdot H_2O$	39,3	4,9	22,9
Vc	243—5*	70—75	51,2	5,1	17,5	$C_{17}H_{21}N_5O_2Cl_2$	51,1	5,3	17,6
Vd	204—5 (Ethanol—DMF)	40—45	44,6	5,1	23,5	$C_9H_{12}N_4O_4$	45,0	5,0	23,3
VI	240—1 (Ethanol—water)	70—75	46,2	4,0	27,3	$C_8H_8N_4O_3$	46,1	3,8	26,9
VII	270—2*	50—55	49,9	4,5	21,0	$C_{17}H_{18}N_6O_2Cl_2$	49,9	4,4	20,6
VIII	102—3 Ethanol	60—65	33,6	3,2	28,7	$C_8H_{10}N_6O_5 \cdot H_2O$	33,9	4,4	29,1

*From DMF.

1,4,5,6,7,8-Hexahydro-3-nitromethyl-4-hydroxy-6,8-dimethylpyrimido[5,4-e][1,2,4]-triazine-5,7-dione (VIII). Compound (III) (0.5 g, 2.5 mmole) was dissolved in 5 ml of water and 1 ml of concentrated hydrochloric acid. To the resulting solution was added 0.5 g (3.9 mmole) of the potassium salt of nitroacetaldehyde, and the mixture stirred for 10 min at 20-25°C. The precipitated (VIII) was filtered off.

3-[p-(Di-2-chloroethyl)aminophenyl]-5,6,7,8-tetrahydro-6,8-dimethylpyrimido[5,4-e][1,2,4]-triazine-5,7-dione (VII). A mixture of 0.2 g (1.0 mmole) of (III) and 0.3 g (1.2 mmole) of p-(di-2-chloroethyl)aminobenzaldehyde was boiled in 10 ml of ethanol and 1 ml of concentrated HCl for 30 min. The mixture was cooled, and the precipitated (VII) filtered off.

Nitrosation of Hydrazone (Vb). To 0.6 g (2.5 mmole) of the hydrazone (Vb) in 10 ml of acetic acid at 15°C was added dropwise 0.5 g (7.2 mmole) of sodium nitrite in 1.5 ml of water. The mixture was stirred for 35-40 min at 20-25°C, then heated to 70-75°C and kept at this temperature for 30 min. The solvent was removed *in vacuo* and the syrupy residue was treated with 5 ml of water. The solid which separated was filtered off and recrystallized from water to give 0.23 g (45%) of (IX). Evaporation of the mother liquors afforded 0.02 g (4%) of (I). Compounds (IX) and (I) were identical with phervenulin 4-oxide and phervenulin, respectively, obtained as described in [4].

EXPERIMENTAL BIOLOGY

The pharmacological studies were designed to detect antiinflammatory, analgesic, or antimicrobial activity in the test compounds.

The studies were carried out in white mongrel mice of both sexes weighing 20 ± 2 g, and Wistar strain white rats weighing 180 ± 30 g, by intraperitoneal administration.

The test compounds were administered as suspensions in 2% starch mucilage, in doses of 1/5 of the LD_{50}.

Antiinflammatory activity was studied in the formalin inflammation model. An oncometric method was used to measure the magnitude of the inflammatory reaction [5].

Analgesic activity was determined using the "hot rod" method [6].

Studies of antimicrobial activity in the compounds were carried out by twofold serial dilution [7] against the bacteria *Staph. aureus* strain 209 and *E. coli* strain M-17.

The studies showed that (II), (LD_{50} 500 mg/kg), (Va) (LD_{50} 500 mg/kg), and (III) (LD_{50} 80 mg/kg) had only weak analgesic activity.

Compound (III) had considerable phlogolytic activity, on the order of amidopyrine, but (II) and (Va) had only weak phlogolytic activity.

Antimicrobial activity was also shown by (II) and (III), being highest in (II). Thus, the minimum bacteriostatic concentration (MBSC) of this compound against *Staph. aureus* was 250 µg/ml, and against *E. coli* it was 500 µg/ml. The minimum bactericidal concentration (MBC) of (II) against *Staph. aureus* was 500 µg/ml, and against *E. coli* it was 1000 µg/ml. The bactericidal activity of (V) against both *Staph. aureus* and *E. coli* was 1000 µg/ml.

These studies show that the search for biologically active compounds in the pyrimidotriazine series holds promise, and is useful in studying the mechanism of the biological effects.

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SYNTHESIS AND BACTERICIDAL ACTIVITY OF FERROCENE-CONTAINING DI- AND TETRAHYDROXYLIC ACETYLENIC ALCOHOLS

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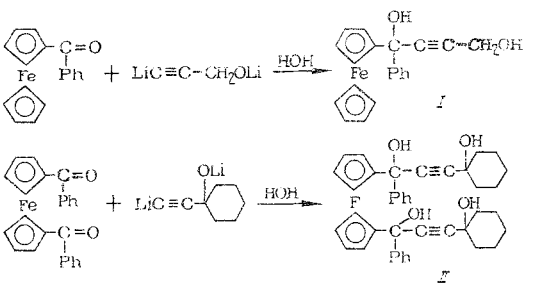
We have previously observed that dihydroxyacetylenic derivatives of ferrocene [1] exhibit antitumor and antioxidant properties [2], and in addition they influence changes in the physicochemical properties of chick embryo cell cultures and are cell growth inhibitors [3].

The aim of this investigation was to synthesize ferrocene-containing di- and tetrahydroxylic alcohols of the acetylene series, and to study their physicochemical and bactericidal properties. In order to synthesize these compounds, the reactions of mono- and dibenzoylferrocene with metal derivatives of acetylenic alcohols were examined. It was found that mono- and dibenzoylferrocene fail to react with magnesium bromide derivatives of acetylenic alcohols either in nucleophilic (ether or tetrahydrofuran) or nonpolar solvents (benzene or toluene). In tetrahydrofuran solution, however, mono- and dibenzoylferrocene react readily with lithium derivatives of acetylenic carbinols, which are known to be reactive in reactions with sterically hindered carbonyl compounds.



The compositions and structures of the compounds obtained (I, II) were established by their elemental analyses and IR spectra. The IR spectra of (I) and (II) show absorption at 3200-3600 cm^{-1} (OH), 3110 cm^{-1} (ferrocene C–H), and weak absorption at 2225-2220 cm^{-1} (C≡C).

EXPERIMENTAL CHEMISTRY

IR spectra were obtained on a UR-20 instrument (East Germany) in vaseline oil and KBr disks.

1-Ferrocenyl-1-phenyl-1,4-dihydroxy-2-butyne (I). To a solution of n-butyllithium (from 2 g of Li and 15 g of butyl chloride) in 100 ml of dry ether was added with stirring under helium a solution of 4 g of propargyl alcohol in 50 ml of dry tetrahydrofuran. The mixture was stirred at room temperature for 1 h. A solution of 10 g of benzoylferrocene in 300 ml of dry tetrahydrofuran was then added, the mixture boiled for 4 h, and the product hydrolyzed by pouring onto ice. It was then extracted with ether, the ether extract washed with water, dried over Na_2SO_4, and the solvent distilled off under reduced pressure to give yellow crystals. These were washed with hexane and recrystallized from benzene to give

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