4,4'-Dibenzylamino-5,6-benzo-2,2'-diquinolyl (IIIb) was obtained in a similar manner by boiling compound II at 180°C and crystallization from toluene. IR spectrum: 3360 (NH); 3030 (CH); 1600, 1580, 1500 (C=C; C=N); 2092 cm^{-1} (CH_2).

4,4'-Diphenoxy-5,6-benzo-2,2'-diquinolyl (IIIc). A 1.9 g portion (5 mmoles) of compound II was added to a solution of sodium phenolate (3 g of metallic sodium and 20 g of phenol) in 120 ml of dry dimethyl sulfoxide, and the mixture was heated for 1 h at 140°C. The dark red solution was poured onto ice, the reaction product was filtered, washed with water, and crystallized from benzene. IR spectrum: 3060 (CH); 1596, 1570, 1480 (C=C; C=N); 1246 cm^{-1} (C–O–).

4,4'-Dithiophenoxy-5,6-benzo-2,2'-diquinolyl (IIId). A mixture of 1.9 g (5 mmoles) of compound II and 30 ml of thiophenol was heated for 3 h at 170°C. After cooling, the reaction mixture was poured into 500 ml of absolute ethanol. The precipitate that separated out was filtered off, washed with alcohol, water, and crystallized from dioxane. IR spectrum: 3060 (CH); 1590, 1570, 1473 cm^{-1} (C=C; C=N).

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SYNTHESIS OF PYRIDO[2,3-d]PYRIMIDINE-2,4-DIONES FROM PYRIMIDO-[4,5-e]-1,2,4-TRIAZINE-6,8-DIONES BY REVERSED AZADIENE SYNTHESIS*

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It was shown that pyrimido[4,5-e]-1,2,4-triazine-6,8-diones enter the reversed azadiene synthesis reaction with ketones and vinyl ethyl ether in the presence of diethylamine or boron trifluoride etherate, and also with enamines. As a result of the reaction, pyrido[2,3-d]pyrimidine-2,4-diones are formed in good yield. Pyrimido[5,4-e]-1,2,4-triazine-5,7-diones do not undergo such reactions with acetone. The reasons for the unique behavior of the isomeric pyrimidotriazinediones in the reaction with acetone are discussed.

Recently interest has increased noticeably with respect to the reversed azadiene synthesis reactions, with which numerous compounds with a very complex structure can be synthesized, which are often unobtainable by other methods [2-4]. As the azadiene component, 1,2,4-triazines among other compounds are particularly widely used, giving in the reaction with electron-donor dienophiles, derivatives of pyridine, pyrimidine and 1,3,5-triazine. Until recently it was not possible to involve condensed aromatic systems in this reaction. We have

*For a preliminary communication, see [1].

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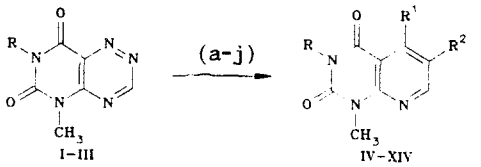
now discovered the first type of condensed aromatic triazines that can undergo these transformations.*

It was found that pyrimido[4,5-e]-1,2,4-triazine-6,8(5H,7H)-diones (I-III), which are structural analogs of the fervenulin antibiotic [6], react with ketones, enamines or vinyl ether with splitting off of nitrogen and formation of the corresponding pyrido[2,3-d]pyrimidine-2,4(1H,3H)diones (IV-XIV). The reaction is catalyzed by diethylamine, triethylamine, and in the case of ketones, by boron trifluoride etherate as well. It is clear that under these conditions, enamines or enols are formed from ketones and vinyl ethyl ether (Table 1), which also perform the role of active dienophiles. The formation of enamines is indicated by the fact that if instead of a cyclopentanone – diethylamine or cyclohexanone – diethylamine mixture, an actual enamine (d' or e') is used in the reaction, the reaction proceeds just as easily.



I–III IV–XIV

I R=CH_3; II R=C_2H_5; III R=$C_6H_5CH_2$; IV R=R^1=CH_3, R^2=H; V R=R^1=R^2=CH_3; VI R=CH_3, R^1=C_2H_5, R^2=H; VII R=CH_3, R^1–R^2=—$(CH_2)_3$—; VIII R=CH_3, R^1–R^2=—$(CH_2)_4$—; IX R=R^1=CH_3, R^2=$COCH_3$; X R=R^1=CH_3, R^2=$CO_2C_2H_5$; XI R=CH_3, R^1=C_6H_5, R^2=H; XII R=CH_3, R^1=R^2=H; XIII R=C_2H_5, R^1=R^2=H; XIV R=$C_6H_5CH_2$, R^1=R^2=H. the designations of dienophiles a-j are given in Table 1.

On the other hand, if diethylamine is replaced by triethylamine, which cannot produce an enamine, the process is strongly retarded. Thus, the time of half-conversion of isofervenulin I into 1,3,5-trimethylpyrido[2,3-d]pyrimidine-2,4-dione (IV) with an equimolar amount of diethylamine in an excess of acetone at 20°C is 23 h according to ^{1}H NMR spectral data. Under the same conditions, with triethylamine, the I → IV half-conversion time is 240 h. In the presence of triethylamine, the reaction most probably proceeds via an enolate anion of acetone a', the concentration of which is very low because of the low acidity of acetone (pK_a 20) [7].†

Compound IV can be obtained on a preparative scale in 94% yield by boiling isofervenulin I with a 36-fold excess of diethyl amine in acetone for 1 h 30 min. At room temperature, the reaction is completed in 3 h, but in this case, together with compound IV (yield 65%), a further very unexpected product is formed – 1,3-dimethylpyrido[2,3-d]pyrimidine-2,4-dione (XII) (yield 17%). We shall discuss the mechanism of its formation in the next article. When an equimolar ratio of isofervenulin and diethylamine in acetone was used, the formation of XII was not observed, and the rate of formation of compound IV substantially decreased; the yield was 55% after 19 h of stirring at 20°C.

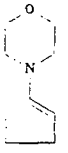
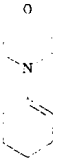
The structure of compound IV was established from the analysis of the ^{1}H and ^{13}C NMR spectrum data, and also from the high resolution mass spectrum data. The values of the chemical shifts and the SSCC of aromatic and C-methyl protons in the ^{1}H NMR spectrum unequivocally prove the γ-position of the methyl group in the aromatic pyridine ring. Thus, the 6-H and 7-H methine aromatic protons are recorded at δ 6.97 and 8.43 ppm, respectively. The 6-H proton signal has a doublet-quartet structure due to the spin-spin interaction with the 7-H proton with a vicinal constant of $J_{6,7}$ = 5.1 Hz, and with the methyl group protons with a distant interaction constant of $^4J_{CH_3,6}$ = 0.6 Hz, while the 7-H signal has a doublet structure with the corresponding vicinal constant. The presence of a spin-spin interaction of the methyl protons and the 6-H proton was confirmed by a double resonance experiment. The values of the chemical shifts and the vicinal constants of the 6-H and 7-H protons completely conform with similar parameters for the β- and α-protons of γ-picoline [8].

The structure of compound XII was established from the ^{1}H and ^{13}C NMR and high resolution mass-spectrometric data (see the experimental part).

*After our investigation had been completed, an article by American authors appeared [5], reporting success in one case in introducing in a low yield a derivative of pyrimido[4,5-e]-1,2,4-triazin-8-one into the reversed azadiene synthesis reaction.

†The participation of enolate anions f' and g' can be more appreciable in the case of acetylacetone (pK_a 9) and acetoacetic ester (pK_a 10.7) [10] (see below).

TABLE 1. Dienophiles Used in the Azadiene Synthesis Reaction

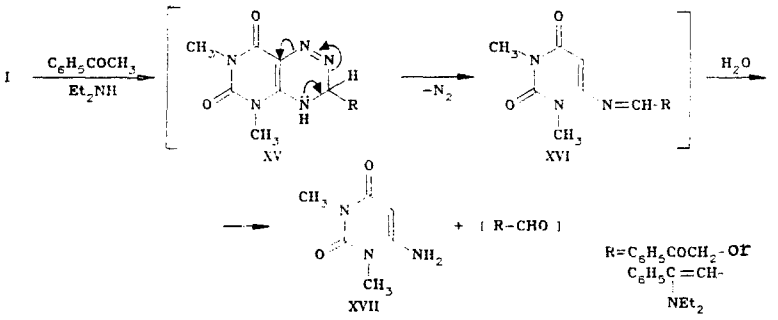
Dienophile		Source of generation	Catalyst
$CH_2=C(NEt_2)-CH_3$	(a)	Acetone	Et_2NH
$CH_2=C(O^-)-CH_3$	(a')	Acetone	Et_3N
$CH_2=C(OH)-CH_3$	(a'')	Acetone	$Et_2O\cdot BF_3$
$CH_2=C(NEt_2)-CH_2CH_3$	(b)	Methyl ethyl ketone	Et_2NH
$CH_3-C(NEt_2)=CH-CH_3$	(b')	Methyl ethyl ketone	Et_2NH
$CH_2=C(OH)-CH_2CH_3$	(c)	Methyl ethyl ketone	$Et_2O\cdot BF_3$
$CH_3-C(OH)=CH-CH_3$	(c')	Methyl ethyl ketone	$Et_2O\cdot BF_3$
	(d)	Cyclopentanone	Et_2NH
	(d')	—	—
	(e)	Cyclohexanone	Et_2NH
	(e')	—	—
$CH_3-C(NEt_2)=CH-COCH_3$	(f)	Acetylacetone	Et_2NH
$CH_3-C(O^-)=CH-COCH_3$	(f')	Acetylacetone	Et_2NH
$CH_3-C(NEt_2)=CH-CO_2Et$	(g)	Acetoacetic ester	Et_2NH
$CH_3-C(O^-)=CH-CO_2Et$	(g')	Acetoacetic ester	Et_2NH
$CH_2=C(NEt_2)-C_6H_5$	(h)	Acetophenone	Et_2NH
$CH_2=CH-NEt_2$	(i)	Vinyl ethyl ether	Et_2NH
$CH_2=CH-NHEt$	(j)	Diethylamine	Et_2NH

In the reaction of compound I with methyl ethyl ketone, two paths of $[4\pi + 2\pi]$-cycloaddition reaction are possible, since the enolization of this ketone may proceed both at the expense of the α-CH_3 group and the methylene unit [dienophiles c and c' (Table 1)]. In fact, the reaction of compound I with methyl ethyl ketone in the presence of diethylamine leads to the formation of two products – 1,3,5,6-tetramethylpyrido[2,3-d]pyrimidine-2,4-dione (V) and

its analog VI with a 5-ethyl group. The ratio of compounds V and VI, obtained in an overall yield of 91%, is 57:43, according to the ^1H NMR spectroscopy data. The two compounds have similar R_f values in various systems of solvents. Only after triple recrystallization of the mixture from ethanol, it was possible to obtain compound V in a pure state. A pure compound VII could not be obtained. When diethylamine is replaced in this reaction by boron trifluoride etherate, the process proceeds in one single direction, and compound V is only obtained in an 80% yield. This result conforms with the known fact of enolization of methyl ethyl ketone in the presence of acid catalysts preferentially to enol c', but not c (see, for example, [9]). At the same time, because of the similar CH-acidity of the α-CH_3 and CH_2 groups [10] enamines b and b' form by the action of diethylamine in commensurable amounts, which also explains the fact of the formation of compounds V and VI in this case in an approximate 1:1 ratio.

The reaction of compound I with cyclopentanone and cyclohexanone in the presence of diethylamine leads to the formation of compounds VII and VIII, respectively, in high yields. The same result is obtained when these ketones are replaced by their enamines d' and e'. In the reaction of isofervenulin I with acetylacetone and acetoacetic ester in the presence of diethylamine, pyrido[2,3-d]pyrimidine-2,4-diones IX and X are formed, which contain an acetyl and ethoxycarbonyl group, respectively, at the 6-position. It is clear that in this case, the corresponding dienophiles have the structures f and g, but the participation of the enolate-anions f' and g' is just as probable, since the reaction proceeds also readily when diethylamine is replaced by triethylamine.

The reaction with acetophenone proceeds with greater difficulty and uniquely. Under mild conditions in the presence of diethylamine, compound I does not react with acetophenone. The reaction proceeds only on heating the solution of compound I in acetophenone at 100-110°C in the presence of diethylamine. 1,3-Dimethyl-5-phenylpyrido[2,3-d]pyrimidine-2,4-dione (XI) is formed as the main reaction product (yield 56%), and 1,3-dimethyl-6-aminouracil (XVII) was isolated as a by-product (yield 19%). The formation of amine XVII is probably due to the fine features of the cycloaddition, in particular, it depends on whether it proceeds synchronously or stagewise. It can be assumed, that irrespective of the form in which acetophenone participates in the reaction (enamine or enolate-anion), the addition of the α-carbon atom fragment of acetophenone to the $C_{(8a)}$ atom of the pyrimidotriazine system is hindered* and the reaction is inhibited, at the stage of formation of the σ-complex XV. The largest part of the σ-complex converts into compound XI. However, it partly decomposes under fairly rigorous conditions with the elimination of a nitrogen molecule and formation of imine XVI, which hydrolyzes further to amine XVII.

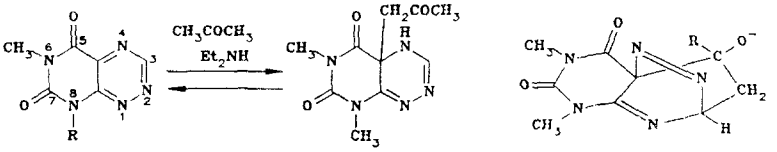


The method of synthesis that we have developed is also suitable for the preparation of pyrido[2,3-d]pyrimidine-2,4-diones, which do not contain substituents in the pyridine ring. When vinyl ethyl ether was used as the dienophile component, we were able to obtain compound XII, as well as its analogs XIII and XIV with ethyl and benzyl groups in the 3-position. It should be emphasized that vinyl ethyl ether itself does not react with compounds I-III. The reaction proceeds only in the presence of diethylamine. It is probable that in this case the enamine is the true dienophile (Table 1), which forms in equilibrium amounts in the reaction of vinyl ethyl ether with diethylamine. In the reaction of isofervenulin I with

*The phenyl group substantially decreases the activity of inamines and enamines [11] in the reversed diene synthesis reactions due to the electron-acceptor action, and possibly, steric factors.

acetaldehyde in the presence of diethylamine or boron trifluoride etherate, only resinification of the reaction mixture was observed.

It was of interest to extend the azadiene synthesis to the pyrimido[5,4-e]-1,2,4-triazine-5,7-diones as well, in particular to the reumycin (XVIII) and fervenulin (XIX) antibiotics. In this case the reaction products could be pyrido[3,2-d]pyrimidine-2,4-diones isomeric with compounds IV-XIV. However, we have found that compounds XVIII and XIX react with acetone very slowly in the presence of diethylamine. In the case of fervenulin, the product of the addition of the acetonyl residue at the 4a position of (XX) could be isolated from the reaction mixture in a crystalline state. Its structure has been established from the ^{1}H NMR, UV and high resolution mass spectrum, although the preferential position of the NH proton [at $N_{(2)}$, or $N_{(4)}$] has not been accurately established. It was noted that in the solution the addition of acetone to fervenulin in the presence of diethylamine is reversible, and the concentration of adduct XX under equilibrium conditions is not higher than 35%.

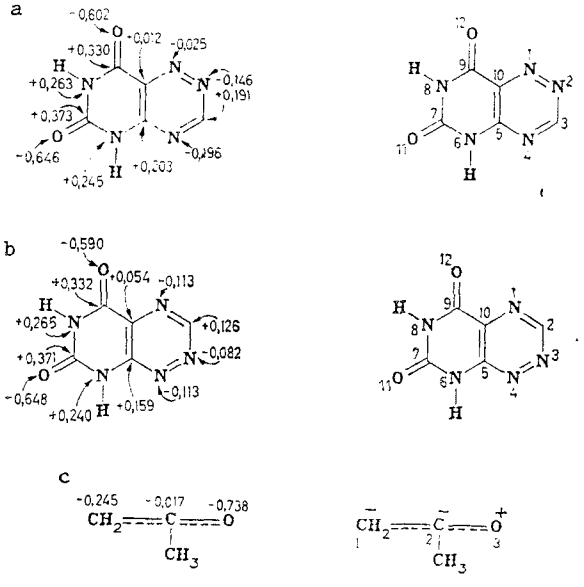


XVIII R=H;
XIX R=CH$_3$

XX

XXI

To explain the reasons for the inertness of reumycin and fervernulin in the reversed azadiene synthesis reaction, we carried out a quantum chemical calculation of the corresponding systems according to the Huckel method (the methyl groups were not taken into account). Calculations (Fig. 1) showed that for isofervenulins, the (4π + 2π)-cycloaddition at the 3- and 8a-positions is allowed from the symmetry standpoint, while for reumycin and fervenulin it is forbidden. As known [12, 13] the reversed azadiene synthesis reaction is controlled by the LFMO* symmetry of the diene (in our case, for compounds I-III) and HOMO* symmetry of the dienophile. Calculation shows that the signs of the coefficients at the atomic orbitals of $C_{(3)}$ and $C_{(8a)}$ for the LFMO of the isofervenulin molecule are the same – similarly as the signs at the atomic orbitals of $C_{(1)}$ and $C_{(2)}$ for the HOMO of the acetone enolate anion or its enamine. This should assist in the creation of a cyclic transition state and formation of an adduct of the type of XXI.



$$\Psi_{LFMO} = -0.5118\psi_1 + 0.1803\psi_2 + 0.3517\psi_3 - 0.3167\psi_4 - 0.0706\psi_5 + 0.0876\psi_6 - 0.1360\psi_7 - 0.1442\psi_8 + 0.4763\psi_9 + 0.2740\psi_{10} + 0.0980\psi_{11} - 0.3432\psi_{12}.$$

$$\Psi_{LFMO} = 0.4314\psi_1 - 0.0231\psi_2 - 0.4241\psi_3 + 0.3681\psi_4 + 0.1247\psi_5 - 0.0933\psi_6 + 0.1005\psi_7 + 0.1556\psi_8 - 0.4534\psi_9 - 0.3277\psi_{10} - 0.0765\psi_{11} + 0.3452\psi_{12}.$$

*LFMO – lower free MO, HOMO – higher occupied MO.

d

$$\Psi_{HOMO} = -0.6678\psi_1 - 0.2172\psi_2 + 0.7118\psi_3.$$
$$\Psi_{HOMO} = 0.7716\psi_1 + 0.4724\psi_2 - 0.4257\psi_3.$$

Effective charges and symmetry of boundary orbitals of isofervenulin (a), fervenulin (b), enolate anion of acetone (c), and enamine (d). The numeration of atoms used in the calculation is shown in the formulas on the right hand side.

Contrary to this, for the fervenulin system, the signs of the coefficients at the atomic orbitals of $C_{(3)}$ and $C_{(8a)}$ atoms for the LFMO are opposite, which makes the cycloaddition unfavorable with respect to the symmetry. It is probable that the values of the effective atomic charges play a substantial role in the determination of the direction and ease of occurrence of the reaction. Thus, the positive π-charge on the $C_{(3)}$ atom of the fervenulin molecule is much lower than in the isofervenulin molecule. In the enolate anion or in the acetone enamine, the negative charge on the terminal carbon atom is much higher than on the central carbon atom of the heteroallyl system. Therefore, during the cycloaddition, it is the terminal carbon atom which adds to the more electron-deficient $C_{(3)}$ atom in isofervenulin. This also accounts for [12] the presence of the methyl and phenyl groups at the γ-position of the pyridine ring in compounds IV-XI, i.e., the high regioselectivity of the reaction.

The new method of synthesis of pyrido[2,3-d]pyrimidine-2,4-diones is obviously important preparatively. For example, compounds IV and XI were previously obtained only in a yield of 20-30% by the reaction of 1,3-dimethyl-6-aminouracil with croton- and cinnamaldehydes, respectively [14]. Moreover, the ready availability of compound I, which can be prepared in two steps from theophylline [15], is also quite an important factor.

EXPERIMENTAL

The IR spectra were run in mineral oil on a UR-20 spectrophotometer, the UV spectra — on a Specord 40 M and SP 8-100 Pye Unicam spectrophotometers. The ^1H and ^{13}C NMR spectra were recorded for ~2 (^1H) and ~15% (^{13}C) solutions of the compounds on a Bruker WH-90 spectrometer with a working frequency of 90 (^1H) and 22.62 (^{13}C) MHz at 30°C. The chemical shifts were measured on a δ scale relative to TMS as internal standard (^1H, δ 0.00 ppm), or relative to the solvent signals of $CDCl_3$ (^{13}C, δ 77.0 ppm) and DMSO-D_6 (^{13}C, δ 39.7 ppm). The mass spectra were obtained on a MAT-311A spectrometer with the direct introduction of the sample into the ionic source. The accelerating voltage was 3.0 kV, the ionizing voltage 70 eV, the cathode emission current 1.0 mA, and the temperature of the ionization chamber was 150°C.

The quantum-chemical calculations for the pyrimido[4,5-e]- and [5,4-e]-1,2,4-triazinedione systems were carried out by the simplified Hückel MO method with the following parametrization [16]: $h_{\dot{N}} = +0.5$; $h_{\ddot{N}} = +1.5$; $h_{\dot{O}} = +1.0$; $k_{C-\dot{N}} = k_{\dot{N}-\ddot{N}} = k_{C=\dot{N}} = 0.8$; $k_{C=O} = 1.0$ (the N-methyl groups were not taken into account). In the calculation of the acetone enolate anion and enamine, the induction model of the methyl group and the following parameters were used; for the enolate $h_{C_{(1)}} = -0.5$; $h_{C_{(2)}} = -0.3$; $h_O = +0.1$; $k_{C-O} = 0.1$; for the enamine $h_{C_{(1)}} = 0.0$; $h_{C_{(2)}\parallel} = -0.3$; $h_{\ddot{N}} = 1.5$; $k_{C-N} = 0.8$; $k_{C-C} = 1.0$.

The chromatography was carried out on Al_2O_3 III grade of activity according to Brockman. The physicochemical characteristics of compounds IV-XIV are given in Table 2. The elemental analysis data for C, H, N correspond to the calculated values.

5-Methyl-7-ethylpyrimido[4,5-e]-1,2,4-triazine-6,8-dione (II, $C_8H_9N_5O_2$). Lead tetraacetate (2.2 g, 5 mmoles) was added in portions in the course of 15 min to a suspension of 0.84 g (4 mmoles) of 3-methyl-1-ethyl-7-aminoxanthine [17] in 50 ml of methylene chloride. The mixture thereby became yellow, and the precipitate dissolved. After completion of addition, the reaction mixture was stirred for 10 min at 20°C, 6 ml of ethylene glycol was added to remove the excess lead tetraacetate, and after 10 min 200 ml of water was added. The organic layer was separated and the aqueous layer was extracted with methylene chloride (2 × 25 ml). The combined organic solutions were evaporated to dryness, and the residue was re-

TABLE 2. Physicochemical Characteristics of Compounds IV-XIV

Compound	IR spectrum, cm^{-1}		UV spectrum*, λ_{max}, nm (log ε)	^1H NMR spectrum ($CDCl_3$), chemical shift (ppm), multiplicity, SSCC (Hz)				
	ring	C=O		1-CH_3	3-R	5-R	6-R	7-H
IV	1568, 1590	1650, 1694	222 (4,10), 242 (sh 3,46), 306 (3,36)	3,71	3,46	2,84 d $J_{CH_3;\,6\text{-}H}=0,6$	6,97 d.q $J_{6,7}=5,1$, $J_{6\text{-}H;\,CH_3}=0,6$	8,43 d $J_{7,6}=5,1$
V	1568,	1658, 1694	244 (sh 3,51), 316 (3,33)	3,55	3,33	2,68	2,23	8,28
VI	—	—	—	3,61	3,36	1,22 t $J=7,1$ (CH_3); 3,23 q $J=7,1$ (CH_2)	6,95 d $J_{6,7}=4,9$	8,40 d $J_{7,6}=4,9$
VII	1578, 1595	1654, 1698	221 (4,21), 245 (sh 3,58), 318 (3,38)	3,71	3,46	2,19, 2,96, 3,47 m	[—$(CH_2)_3$—]	8,42
VIII	1565, 1585	1651, 1696	224 (4,46), 246 (sh 3,93), 318 (3,70)	3,70	3,45	1,81, 2,79, 3,46 m	[—$(CH_2)_4$—]	8,30
IX	1550, 1580	1650, 1674, 1700	229 (3,90), 272 (3,55), 309 (3,26)	3,73	3,46	2,97	2,63	8,76
X	1560, 1575	1660, 1700	226 (4,03), 268 (3,62), 306 (3,26)	3,72	3,41	3,03	1,38 t $J=7,1$ (CH_3); 4,35 q $J=7,1$ (CH_2)	8,93
XI	1548, 1570, 1612	1654, 1704	234 (sh 3,80), 316 (3,41)	3,83	3,42	7,25 . . . 7,55	7,01 d $J_{6,7}=4,9$	8,65 d $J_{7,6}=4,9$
XII	1592	1653, 1700	224 (4,11), 244 (sh 3,50), 310 (3,39)	3,73	3,49	8,47 dd $J_{5,6}=7,7$, $J_{5,7}=1,9$	7,21 dd $J_{6,5}=7,7$, $J_{6,7}=4,8$	8,66 dd $J_{7,6}=4,8$, $J_{7,5}=1,9$
XIII	1593	1655, 1695	232 (sh 3,59), 243 (sh 3,52), 310 (3,40)	—	—	—	—	—
XIV	1590	1655, 1694	240 (sh 3,51), 309 (3,35)	—	—	—	—	—

*sh. — shoulder.

crystallized from alcohol. Yield, 0.5 g (61%). Light-yellow crystals, mp 112-113°C. IR spectrum: 1532, 1680, 1720 cm^{-1} (C=O). ^1H NMR spectrum (DMSO-D_6): 1.34 (3H, t, J = 7.1 Hz, C–CH_3), 3.68 (3H, s, 5-CH_3), 4.22 (2H, q, J = 7.1 Hz, CH_2), 9.52 (1H, s, 3-H).

5-Methyl-7-benzylpyrimido[4,5-e]-1,2,4-triazine-6,8-dione (III, $C_{13}H_{11}N_5O_2$) was obtained in a similar manner as compound II from 1-benzyl-3-methyl-7-aminoxanthine [17]. Yield 67%. Yellow crystals, mp 145-146°C (from alcohol). IR spectrum: 1530, 1678, 1725 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$): 3.66 (3H, s, 5-CH_3), 5.30 (2H, s, CH_2), 7.25 (5H, m, C_6H_5), 9.50 ppm (1H, s, 3-H).

1,3,5-Trimethylpyrido[2,3-d]pyrimidine-2,4-dione (IV). A. A solution of 0.25 g (1.3 mmole) of compound I and 5.2 ml (44 mmoles) of diethylamine in 15 ml of acetone was boiled for 1 h 30 min. The reaction mixture was evaporated to dryness. The residue was dissolved in 20 ml of chloroform and passed through a column with Al_2O_3, eluting with chloroform. The fraction with R_f was collected. Yield, 0.25 g (94%). Pale-yellow crystals, mp 158-159°C (from alcohol), which corresponds to the literature data [14].

B. A solution of 0.2 g (1 mmole) of compound I and 0.11 ml (1 mmole) of diethylamine in 12 ml of acetone was stirred for 19 h at 20°C. The isolation and purification were carried out in a similar manner as in the preceding experiment. The yield of compound IV was 0.11 g (55%).

C. A solution of 0.17 g (0.9 mmole) of compound I and 4 ml (36 mmoles) of diethylamine in 16 ml of acetone was stirred for 3 h and 20°C, then evaporated, the residue was dissolved in 4 ml of chloroform and chromatographed on 15 glass plates (20 × 20 cm, sorbent Kieselgel 60 PF_{254} with a layer thickness of 0.5 mm) placed in BN chambers, passing through a 3:1 hexane–ethyl acetate mixture of solvents. After three fronts of the solvent system had passed through (timed), the chromatography was discontinued; by eluting with methanol, zones were collected running 11-14 cm (fraction, containing compound IV) and 8-10 cm (fraction containing 1,3-dimethylpyrido-2,3-d]pyrimidine-2,4-dione XII). The eluent was distilled off on a rotary evaporator to yield 0.12 g (65%) of compound IV and 0.03 g (17%) of compound XII. Compound IV – pale-cream-colored crystals, mp 158-159°C (from methanol). ^{13}C NMR spectrum ($CDCl_3$): 22.21 (q.d, ^1J = 129.8, $^3J_{C,6\text{-}H}$ = 5.0 Hz, 5-CH_3), 28.09 (q, ^1J = 142.1 Hz, 3-CH_3), 29.82 (q, ^1J = 142.1 Hz, 1-CH_3), 109.21 (m, $C_{(4a)}$), 122.09 (d.d.q, ^1J = 165.5, $^2J_{C(6),7\text{-}H}$ = 8.3, $^3J_{C(6),5\text{-}CH_3}$ = 5.5 Hz, $C_{(6)}$), 151.12 (m, $C_{(2)}$), 151.77 (d.m, $^3J_{C(8a),7\text{-}H}$ = 13.2 Hz, $C_{(8a)}$), 151.87 (d.d, ^1J = 179.3, $^2J_{C(7),6\text{-}H}$ = 3.9 Hz, $C_{(7)}$) 153.23 (d.q, $^3J_{C(5),7\text{-}H}$ = $^2J_{C(5),5\text{-}CH_3}$ = 6.1 Hz, $C_{(5)}$), 161.84 (m, $C_{(4)}$). Mass spectrum*: 206 (11), 205 (100), 190 (11), 177 (25), 176 (21), 93 (26), 92 (8), 91 (7), 78 (14), 63 (10). High resolution mass spectrum, m/z, exp, m/z calc. (empirical formula): 205.0861, 205.0871 ($C_{10}H_{11}N_3O_2$).

Compound XII – pale-yellow crystals, mp 160-162°C (from methanol). ^{13}C NMR spectrum ($CDCl_3$): 28.43 (3-CH_3), 29.40 (1-CH_3), 110.77 ($C_{(4a)}$), 118.81 ($C_{(6)}$), 137.60 ($C_{(5)}$), 151.09 ($C_{(2)}$), 151.48 ($C_{(8a)}$), 154.04 ($C_{(7)}$), 161.45 ($C_{(4)}$). Mass spectrum: 192 (11), 191 (100), 163 (11), 162 (12), 106 (8), 79 (19), 61 (21). High resolution mass spectrum, m/z, exp., m/z calc. (empirical formula): 191.0705, 191.0695 ($C_9H_9N_3O_2$).

D. A solution of 0.2 g (1 mmole) of compound I and 0.3 g (2.1 mmoles), of boron trifluoride etherate in 10 ml of acetone was boiled for 12 h. Isolation and purification was carried out as in method A. Yield, 0.05 g (25%). Light-cream-colored needles, mp 159-160°C (from alcohol). A 0.15 g portion (74%) of isofervenulin I, mp 212-213°C (from alcohol) was regenerated.

1,3,5,6-Tetramethylpyrido[2,3-d]pyridimine-2,4-dione (V, $C_{11}H_{13}N_3O_2$). A. A solution of 0.4 g (2 mmoles) of isofervenulin I and 0.28 g (2 mmoles) of boron trifluoride etherate in 10 ml of methyl ethyl ketone was boiled for 2 h. The mixture was evaporated to dryness, the residue was treated with 3 ml of 22% NH_4OH, and after drying, was dissolved in 20 ml of chloroform and the solution was passed through a column with Al_2O_3, with elution by chloroform. The fraction with R_f 0.71 was collected. Yield, 0.35 g (80%). Colorless needles, mp 150-152°C (from alcohol).

*For all the ion peaks, here and below the m/z values are given, the relative intensity (%) with respect to the maximal ion peak is given in brackets.

B. A solution of 0.39 g (2 mmoles) of compound I and 0.52 ml (4.4 mmoles) of diethylamine in 10 ml of methyl ethyl ketone was boiled for 3 h. The isolation and purification of the reaction products were carried out in a conventional manner. The yield of a mixture of compound V and 1,3-dimethyl-5-ethylpyrido[2,3-d]pyrimidine-2,4-dione (VI) was 0.4 g (91%). According to the ^1H NMR data, the ratio of compounds V:VI was 57:43. After a triple recrystallization of the mixture from alcohol, only the tetramethyl derivative V, mp 150-151.5°C was isolated.

1,3-Dimethylcyclopento[f]pyrido[2,3-d]pyrimidine-2,4-dione (VII, $C_{12}H_{13}N_3O_2$). A. A solution of 0.39 g (2 mmoles) of compound I and 0.52 ml (4.4 mmoles) of diethylamine in 12 ml of cyclopentanone was boiled for 1 h 30 min. The isolation and purification were carried in a similar manner as in the preceding experiment, R_f 0.64. Yield 0.35 g (76%). Colorless needles, mp 164-165°C (from alcohol).

B. A 20 μliter portion of morpholinocyclopent-1-ene was added to a solution of 20 mg (0.1 mmole) of isofervenulin I in 1.5 ml of methanol. An evolution of a gas was thus observed. After 1 min, the reaction mixture was evaporated to one half of its volume, and cooled to 4°C for 12 h. The precipitate that separated out was filtered off, washed with 1 ml of cold methanol, and dried. Yield, 14 mg (58%). Light-yellow crystals, mp 150-152°C (from methanol). Mass spectrum: 232 (11), 231 (75), 230 (35), 203 (18), 202 (19), 119 (30), 62 (10), 61 (100), 60 (12). High resolution mass spectrum, m/z exp., m/z calc. (empirical formula): 231.0980, 231.1017 ($C_{12}H_{13}N_3O_2$).

1,3-Dimethylcyclohexano[f]pyrido[2,3-d]pyrimidine-2,4-dione (VIII, $C_{13}H_{15}N_3O_2$). (A) was obtained in a similar manner as in the preceding experiment A, yield, 94%. Colorless needles, mp 127-129°C (from alcohol). R_f 0.61.

(B) was obtained in the same manner as in preceding experiment B from 39 mg (0.1 mmole) of compound I and 40 μliter of morpholinocyclohex-1-ene in 3 ml of methanol. Yield, 40 mg (82%). Light-yellow crystals, mp 124-126°C (from methanol). Mass spectrum: 246 (16), 245 (100), 244 (32), 230 (19), 217 (20), 216 (17), 133 (31), 130 (12), 105 (11), 77 (10), 57 (10). High resolution mass spectrum, m/z exp., m/z calc. (empirical formula): 245.1164, 245.1164 ($C_{13}H_{15}N_3O_2$).

1,3,5-Trimethyl-6-acetylpyrido[2,3-d]pyrimidine-2,4-dione (IX, $C_{12}H_{13}N_3O_2$). A solution of 0.4 g (2 mmoles) of compound I and 0.52 ml (4 mmoles) of diethylamine in 8 ml of acetylacetone was boiled for 2 h. After a few min a gas began to evolve from the warm solution. The isolation and purification was carried out in a conventional manner. Yield, 0.47 g (95%). R_f 0.53. Colórless prisms mp 186-187°C (from DMFA).

1,3,5-Trimethyl-6-carbethoxypyrido[2,3-d]pyrimidine-2,4-dione (X, $C_{13}H_{15}N_3O_4$). A solution of 0.39 g (2 mmoles) of compound I and 0.52 ml (4.2 mmoles) of diethylamine in 5 ml of acetoacetic ester was stirred for 2 h at 100-110°C. The mixture was evaporated to dryness, dissolved in 20 ml of chloroform, and purified by chromatography on a column with Al_2O_3 (eluent chloroform). A fraction with R_f 0.68 was collected. Yield 0.4 g (72%). Colorless needles, mp 117-118°C (from alcohol).

1,3-Dimethyl-6-aminouracil (XVII). An 18 ml portion (0.16 mole) of a freshly distilled cyanoacetic ester was added to a solution of 3.8 g (0.16 mole) of sodium in 50 ml of absolute methanol, and then a solution of 12.5 g (0.15 mole) of N,N'dimethylurea in 15 ml of absolute methanol was added dropwise. The mixture was boiled for 5 h, and after cooling, a precipitate of the sodium salt of 1,3-dimethyl-6-aminouracil was filtered off and washed with methanol. The salt was suspended in 50 ml of water and treated with acetic acid to pH 4-5. The mixture was cooled and a precipitate was filtered off and was washed with water and alcohol. Yield 9.1 g (36%). Sand colored needles, mp 294-296°C (from water). IR spectrum: 1577; 1610, 1650 (C=O); 3228, 3348, 3390 cm^{-1} (NH, H_2O). PMR spectrum (DMSO-D_6): 3.07 (3H, s, CH_3), 3.24 (3H, s, CH_3), 4.69 (1H, s, 5-H), 6.73 ppm, (br. NH_2). ^{13}C NMR spectrum (DMSO-D_6): 27.16 (1-CH_3), 29.40 (3-CH_3), 75.11 ($C_{(5)}$), 151.85 ($C_{(6)}$), 155.11 ($C_{(2)}$), 161.66 ($C_{(4)}$).

1,3-Dimethyl-5-phenylpyrido[2,3-d]pyrimidine-2,4-dione (XI). A solution of 0.39 g (2 mmoles) of compound I and 0.52 ml (4 mmoles) of diethylamine in 5 ml (43 mmoles) of acetophenone was stirred for 3 h at 100-110°C. After 1 h, a yellowish precipitate began to separate from the hot solution, which after cooling was filtered and washed with chloroform. The yield of 1,3-dimethyl-6-aminouracil was 0.06 g (19%). Pale-yellow crystals, mp 293-294°C (from water). In all its physicochemical properties this compound was identical with the

product obtained by the preceding procedure. The solution of compound XI in acetophenone was evaporated to dryness, the residue was dissolved in 20 ml of chloroform, and purified chromatographically on a column with Al_2O_3 (eluent chloroform). R_f 0.81. Yield, 0.3 g (56%). Pale-yellow crystals, mp 186-187°C (from alcohol), which corresponds to the literature data [14].

1,3-Dimethylpyrido[2,3-d]pyrimidine-2,4-dione (XII). A solution of 0.2 g (1 mmole) of isofervenulin I, 0.26 ml (2.1 mmoles) of diethylamine and 8 ml (83 mmoles) of vinyl ethyl ether in 5 ml of methanol was boiled for 3 h. The mixture was evaporated to dryness, and the residue after being dissolved in chloroform, was passed through a column with Al_2O_3 (eluent chloroform), collecting the fraction with R_f 0.74. Yield, 0.14 g (73%). Light-yellow needles, mp 163-164°C (from alcohol), which corresponds to the literature data.

1-Methyl-3-ethylpyrido[2,3-d]pyrimidine-2,4-dione (XIII, $C_{10}H_{11}N_3O_2$). A solution of 0.21 g (1 mmole) of compound II, 0.26 ml (2.1 mmoles) of diethylamine and 5 ml (52 mmoles) of vinyl ethyl ether in 5 ml of methanol was boiled for 5 h. The product was purified chromatographically on a column with Al_2O_3 (eluent chloroform), R_f 0.82. Yield, 0.07 g (35%). Colorless needles, mp 78-80°C (from alcohol).

1-Methyl-3-benzylpyrido[2,3-d]pyrimidine-2,4-dione (XIV, $C_{15}H_{13}N_3O_2$) was obtained in a similar manner as compound XIII, yield 59%, R_f 0.76. Colorless crystals, mp 100-102°C (from alcohol).

4a-Acetonyl-4,4a-dihydro-6,8-dimethylpyrimido[5,4-e]-1,2,4-triazine-5,7(6H,8H)-dione (XX, $C_{10}H_{13}N_5O_3$). A 0.5 ml portion of diethylamine was added to a solution of 19 mg (0.1 mmole) of fervenulin XIX in 0.5 ml of acetone. After 24 h, the reaction mixture was evaporated on a rotary evaporator. The residue was dissolved in 1 ml of chloroform and chromatographed on a column (60 × 7 mm) with silica gel L 40/100. First, 5 ml of chloroform elute 12 mg of fervernulin, and then by elution with 5 ml of a 10:1 chloroform–methanol solvent mixture, followed by chromatography on a 20 × 20 cm glass plate (Kieselgel 40 PF_{254}), placed in a BN chamber, by passing through a 20:1 chloroform–methanol solvent mixture, 3 mg (12%) of 4a-acetonylfervenulin XX was obtained, mp 138-140°C (from methanol). UV spectrum (water, pH 6.0), λ_{max} (log ε): 240 nm (sh. 3.53), 290 nm (3.41). ^1H NMR ($CDCl_3$): 2.06 (3H, s, C–CH_3), 2.8-3.2 (2H, AB system, CH_2), 3.31 (3H, s, N–CH_3), 3.34 (3H, s, N–CH_3), 7.51 ppm (1H, br. 3-H). Mass spectrum: 251 (9), 208 (5), 195 (10), 194 (100), 193 (12), 166 (21), 151 (10), 137 (23), 124 (9), 82 (12), 68 (12), 67 (16), 66 (12), 58 (12). High resolution mass spectrum, m/z exp., m/z calc. (empirical formula): 251.0985, 251.1018 ($C_{10}H_{13}N_5O_3$).

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