SOME PHYSICOCHEMICAL PROPERTIES OF THE STRUCTURE OF 4a-INDOLYL DERIVATIVES OF FERVENULIN AND ITS 3-SUBSTITUTED ANALOGUES

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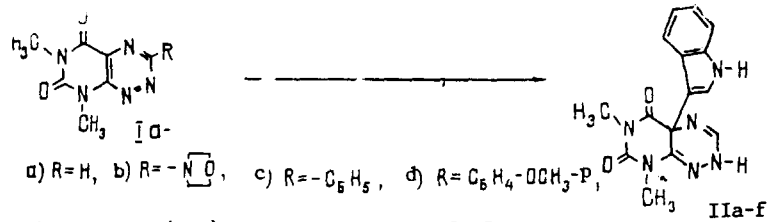
The ^1H and ^{13}C NMR and the IR spectra of the antibiotic fervenulin and its 3-substituted analogues and their 4a-indolyl derivatives are considered. Diagnostic spectral characteristics of the compounds mentioned have been revealed. Information on the structure of the 4a-indolyl derivatives of the fervenulins obtained with the aid of NMR and IR spectroscopies has been confirmed and supplemented by an x-ray structural analysis performed for crystals 4a-(indol-3-yl)-6,8-dimethyl-2,4a-5,6,7,8-hexahydropyrimido[5,4-e][1,2,4]triazine-5,6-dione.

It is known that the antibiotic fervenulin and its 3-alkyl or 3-aryl derivatives are transformed into derivatives of xanthine [1], 6-azapurine [2], or as-triazine [3] as the result of the nucleophilic attack of their pyrimidotriazine nucleus by formamide at C-8a, by the HO^- ion at C-5, and by primary amines at C-7, respectively. Fervenulin and its 3-substituted derivatives react with indole under the conditions of acid catalysis with the formation of 4a-indolyl derivatives [4].

The transformations of the antibiotic fervenulin and its derivatives that have been described may be of interest as routes in the synthetic search for new drugs and also for studying the metabolism and understanding the mechanism of the biological action of these compounds. Accordingly, the task of physicochemical investigations of the products of chemical transformations of the antibiotics may be not only the determination of their structures but also the finding of diagnostic characteristics for these compounds.

We have investigated 4a-indolyl derivatives of the antibiotic fervenulin and its 3-substituted analogues. We had synthesized the majority of these compounds previously [4], but their structures and physicochemical properties had not been investigated in detail.



Ia-f

a) R=H, b) R=-N⟨O⟩, c) R=-C$_6$H$_5$, d) R=C$_6$H$_4$-OCH$_3$-p, e) R=-C$_6$H$_4$ N(CH$_2$)$_2$-p, f) R=-C$_6$H$_4$-NO$_2$-p

IIa-f

The 4a-indolyl derivatives of 3-substituted fervenulins were colorless crystalline substances, in contrast to the colored corresponding initial fervenulins. This indicates a disturbance of the conjugation of the π-system as the result of the addition of indole to the pyridinotriazine nucleus of the fervenulin molecule.

It can be seen from a diagram of the changes in the chemical shifts of the ^{13}C atoms of the pyridinotriazine nucleus (Fig. 1) that a variation in the substituent at the C-3 atom of the initial compounds (I) has a considerable effect on the chemical shift (CS) of this atom and the C-8a atom present in the p-position with respect to it, while the CSs of the C-4a, C-5, and C-7 atoms change insignificantly.

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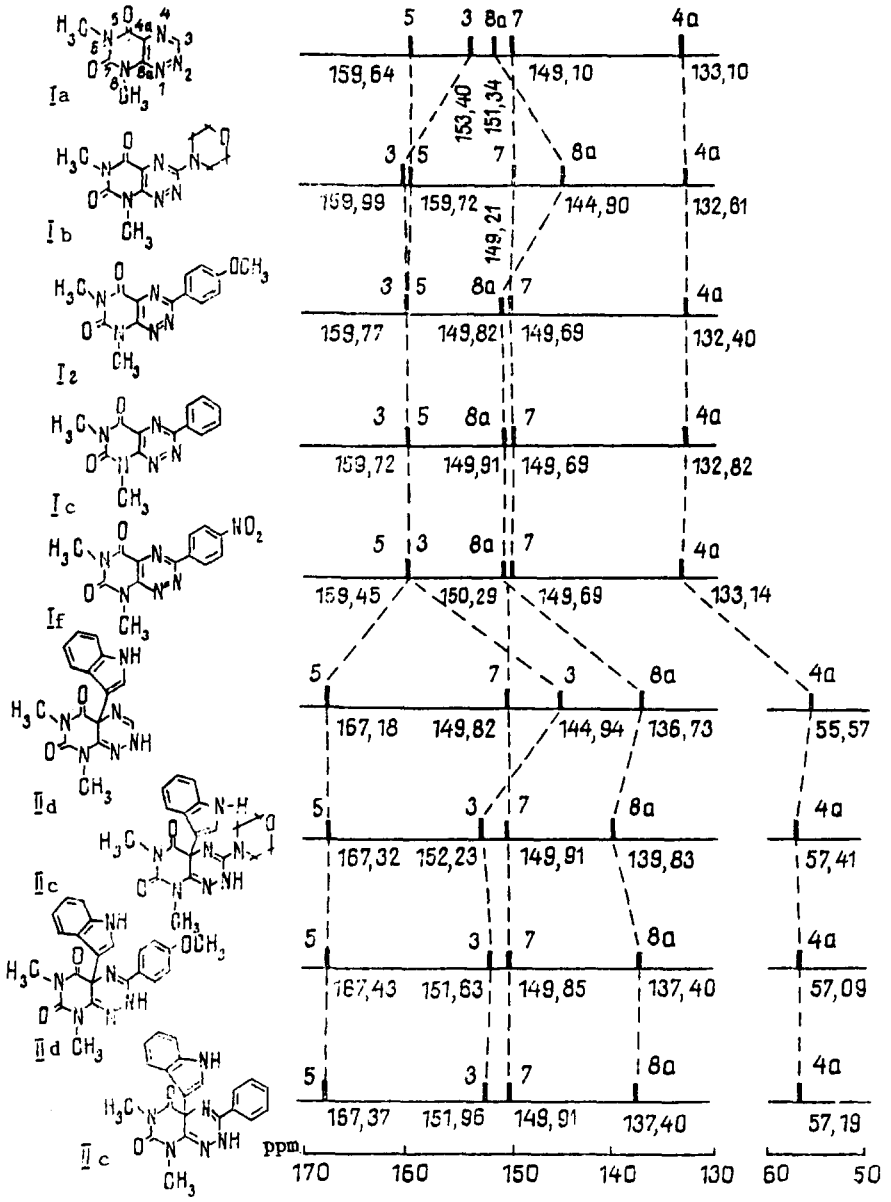

Fig. 1. Chemical shifts of the ^{13}C atoms of the pyridinotriazine nucleus of 3-substituted fervenulins and their 4a-indolyl derivatives.

The addition of indole to the pyridinotriazine nucleus leads to the appearance of a sp^3-hybridized carbon atom the signal of which is observed in the strong field (55-58 ppm). The disruption of the conjugation of the π-system of the triazine ring and the C_5=O group due to the addition of indole at the C-4a atom leads to an increase in the double-bondedness of the C_5=O bond. Under these conditions, the paramagnetic component increases and, accordingly, so does the CS of the C-5 atom (Δδ = 7-8 ppm). The CS of the C-7 atom of the fervenulins (I) scarcely changes on passing to the addition products (II) (Δδ less than 1 ppm). The changes in the CS of the C-3 atom on passing from the initial fervenulins to products (II), depending on the nature of the substituent at this atom, vary between 8 and 9 ppm, and those of the C-8a atom between 5 and 15 ppm.

The signals of the protons of the methyl groups in the PMR spectrum of the initial compounds in DMSO-d_6 are observed in the 3.30-3.39 and 3.61-3.76 ppm regions (Table 1). The H-3 proton of fervenulin resonates at 9.82 ppm. The protons of the N–CH_3 groups in the spectra of products (II) are observed correspondingly at 3.00-3.07 and 3.39-3.45 ppm. The H-3 proton of compound (IIa) is observed at 7.39 ppm. The proton of the 2-NH group

TABLE 1. Parameters of the ^1H NMR Spectra for Solutions of Compounds (I) and (II) in DMSO-d_6 (δ, ppm)

Compound	2-NH	H-3	6-N—CH_3	8-N—CH_3	Prontons of the substitutuent in the trianzine ring	Prontons of the indole fragment	
						NH	CH
Ia	—	9 82	3,33	3,67	—	—	—
Ib	—	—	3,30	3,61	3,8 br.s (8H)	—	—
Ic	—	—	3,38	3,74	7,6—8,4 m (5H)	—	—
Id	—	—	3,37	3,72	3,87 s (3H); 7,15d (2H, J=8,85 Hz); 8,85d (2H, J=8,85 Hz).	—	—
If	—	—	3,39	3,76	8,45 d (2H, J=8,85 Hz); 8,67 d (2H. J=8,85 Hz)	—	—
IIa	10,46	7,39	3,04	3.40	—	11,15	6,90—7,90 m (5H)
IIb	10.20	—	3,02	3 39	3,21 br.s(4H); 3,53 br.s. (4H)	11,09	6,90—7,95 m (5H)
IIc	10,07	—	3,07	3,45	7,40—7,90 m (5H)	11,12	7,00—8,10 m (5H)
IId	10,94	—	3,07	3,44	6,99 d (2H, J=8,77 Hz); 7,85 d (2H, J=8,77 Hz).	11,07	7,00—8,10 m (5H)
IIe	10,76	—	3,07	3,44	2,93 s (3H); 6,70 d (2H, J=8,75 Hz); 7,77 d (2H, J=8.75 Hz).	11,02	7,00—8,10 m (5H)

TABLE 2. IR Spectra of Compound (I) and (II) (ν, cm^{-1})

Compound	$\nu C_5=O$	$\nu C_7=O$	$\nu C=C$ $\nu C=N$	ν NH of the indole fragment	ν NH of the triazine ring
Ia	1728	1703 1695 1680 1675	1583 1580 1540	—	—
Ic	1730	1681 1675	1575 1542	—	—
	1735	1688 1678	1560 1540	—	—
Ie	1733	1682 1671	1570 1543	—	—
If	1730	1690 1680 1670	1570 1534	—	—
IIa	1726	1684	1646 1638	3344	3200 3175
IIc	1723	1682	1656	3390	3300
IId	1722	1682	1648	3401	3266
IIe	1728	1678	1640 1674	3323	3208 3183

of products (II) in DMSO-d_6 resonates at 10.20-11.07 ppm. At the same time, its CS increases in accordance with the electronic properties of the substituents in position 3: NC_4H_8O, H, C_6H_4—$N(CH_3)_2$-p, C_6H_4—OCH_3-p, C_6H_5 (10.20, 10.46, 10.94, 11.07 ppm).

In the IR spectra of crystals of compounds (I) it is possible to see two main adsorption bands of carbonyl groups: one narrow, high-frequency, one, and the other broadened with several submaxima at lower frequencies (Table 2). At the same time, the relative intensity of the low-frequency band considerably exceeds that of the high-frequency band. The low-frequency band obviously corresponds to the absorption of the C_7=O bond, since it is just for this that the largest number of polar resonances is possible. The size of the shift of the $\nu_{C_7=O}$ band in the high-frequency region on passing the solutions in CCl_4 and $CHCl_3$ is smaller than for the $\nu_{C_5=O}$ band, which is likewise a consequence of the greater resonance stabilization. A change in the phase state of the sample has little effect on the positions of the maxima of the absorption band of the conjugated C=C and C=N bonds of the triazine rings of compounds (I). The vibrations of the isolated C—H group of the triazine ring of fervenulin appear clearly in the high-frequency part of the IR spectra in the form of a narrow band at about 3070 cm^{-1}. For the 3-substituted compounds (Ib-f) a shift of the $\nu_{C_5=O}$ band in the higher-frequency direction as compared with fervenulin is observed. It must also be mentioned that the form of the absorption curve of the carbonyl groups of compounds (Ib-f) becomes less complex, and the $\nu_{C_5=O}$ and $\nu_{C_7=O}$ bands are resolved more clearly. This is apparently connected with the denser packing of the large molecules

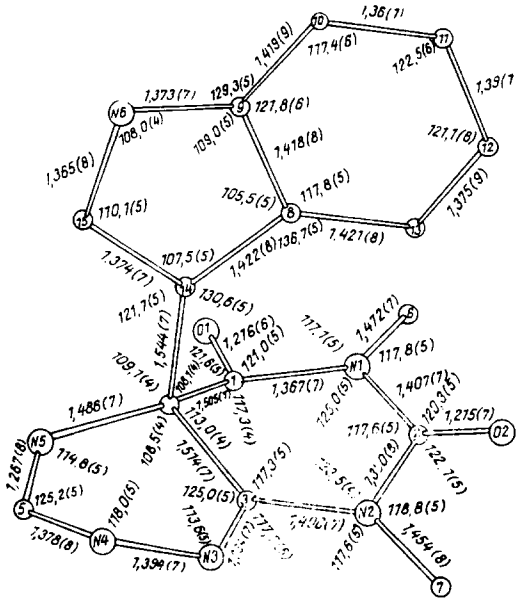

Fig. 2. Structure of the molecule of 4a-(indol-3-yl)-6,8-dimethyl-2,4a,5,6,7,8-hexahydropyridino[5,4-e][1,2,4]triazine-5,7-dione (IIa). The valence angles C3C4C14 and C1C4N5 are 110.2(4) and 107.8(4)°, respectively.

TABLE 3. Coordinates of the Atoms (× 10^4, H × 10^3)

Atom	x	y	z	Atom	x	y	z
O1	3545 (3)	−50 (5)	2261 (4)	C10	2906 (5)	6360 (7)	−184 (6)
O2	442 (3)	1172 (5)	1631 (4)	C11	1924 (5)	6420 (9)	−674 (6)
N1	2001 (3)	567 (5)	1934 (4)	C12	1349 (4)	5558 (8)	−236 (6)
N2	1633 (3)	2637 (5)	2980 (4)	C13	1755 (4)	4591 (7)	733 (5)
N3	2818 (3)	3896 (6)	4489 (4)	C14	3460 (4)	3652 (7)	2274 (5)
N4	3812 (4)	4138 (6)	5075 (4)	C15	4370 (4)	4051 (7)	2346 (5)
N5	4244 (3)	2075 (6)	4085 (4)	H (114)	385	464	584
N6	4304 (3)	5105 (6)	1478 (4)	H (116)	458	548	119
C1	2975 (4)	860 (6)	2419 (5)	H5	515	307	568
C2	1297 (4)	1464 (7)	2156 (5)	H61	112	−86	99
C3	2596 (4)	3022 (6)	3590 (5)	H62	185	−171	156
C4	3305 (3)	2355 (6)	3096 (4)	H63	182	−120	48
C5	4428 (4)	2984 (8)	4964 (5)	H10	340	700	−46
C6	1674 (4)	−838 (7)	1161 (6)	H11	146	685	−145
C7	911 (5)	3464 (9)	3320 (7)	H12	53	561	−67
C8	2779 (4)	4482 (6)	1300 (5)	H13	154	389	125
C9	3341 (4)	5381 (6)	822 (5)	H15	500	382	291

*The values of the parameters of the anisotropic temperature factors of the nonhydrogen atoms can be obtained from the authors.

in the crystal and, in view of this, the smaller degree of intermolecular interaction. The relative intensities of the bands characterizing the systems of conjugation of the C=C and C=N bonds fall appreciably in comparison with unsubstituted fervenulin when electron-donating groups are present in the 3-aryl substituent of compounds (Ic-f) and, conversely, they rise under the influence of the electron accepting NO_2 group. It is obvious that the realization of the electron-donating capacity of the OCH_3 and $N(CH_3)_2$ groups leads to a more uniform distribution of the electron density in the triazine ring of the molecules of (Ib and e), thereby decreasing the polarity of the C=C and C=N bonds. Conversely, the NO_2 group enhances the delocalization of the π-electrons and increases the polarity of the bonds.

In the IR spectra of crystalline samples of the 4a-indolyl derivatives (II) characteristic absorption bands of isolated C=N bonds in the median region (about 1640 cm^{-1}) and of

TABLE 4. Deviations (Å) of the Atoms from the Planes of Some Planar Fragments of the Molecule

Planes	Atoms									
1	N6	C8	C9	C11	C12	C13	C14	C15	C4*	
	,00	,01	,00	,00	,00	,00	,00	−,01	−,10	
2	N1	N2	N3	N4	N5	C1	C2	C3	C5	C4*
	−,07	−,01	−,03	,08	,00	,15	−,10	,16	−,16	,59
3	N1	N2	C1	C2	C3	C4*				
	,03	,00	−,02	−,02	,01	−,35				
4	N3	N4	N5	C3	C5	C4*				
	−,10	,12	,03	,04	−,09	,52				

The planes form the following dihedral angles with one another: 1/2 = 85.8; 1/3 = 91.7; 1/4 = 84.4; 3/4 = 168.0°.
*Atom not included in the calculation of the given plane.

two types of amino groups in the 3320-3400 and 3100-3350 cm^{-1} regions have been singled out [4]. A disturbance of the conjugation of the π-system of the pyridinotriazine nucleus as a consequence of the addition of indole to compounds (I) leads to an increase in the doublet-bondedness both of the C=N bonds [4] and also of the C_5=O bond (as is shown by the NMR results given above). An increase in the frequency of the $\nu_{C_5=O}$ absorption should correspond to this. However, in the IR spectra of solid samples of products (II) there is a relative lowering of the $\nu_{C_5=O}$ frequencies in comparison with the initial compounds (I). This phenomenon is apparently connected with the participation of the oxygen of the C_5=O group in the intermolecular bonds of these compounds.

Conclusions concerning the structure of the indole derivatives made on the basis of a study of the ^1C NMR spectra of their solutions and the IR spectra of crystals of these compounds have been confirmed by the results of an x-ray structural analysis performed for compound (IIa). As a result of the x-ray structural study of crystals of compounds (IIa)* it was established that the five-atom fragments of the six-membered nitrogen-containing heterocycles (without the C4 atom) are almost planar, and the dihedral angle between their planes if 12.0° (Table 3). The plane of the indole fragment is almost normal to these planes and forms angles of 84.4 and 91.7° with them. The torsion angles around the C4–C14 bond describing the mutual orientation of the indole fragment and the three bonds with the participation of the C4 atom are as follows: N5C4C14C15 = 14.1°; C1C4C14C15 = −102.9°; C3C4C14C15 = 133.2°; C1C4C14C8 = 71.2°; N5C4C14C8 = −171.8°; C3C4C14C8 = −52.7°.

The tetrahedral configuration of the C4 atom leads to its substantial displacement (by 0.59 Å) in the direction of the C14 atom of the indole group from the N1-N5, C1C2C3C5 plane. As was assumed from an analysis of the IR spectra, in the molecule of (IIa) there are two isolated C=N bonds: C5=N5 and C3=N3 (1.267 and 1.264 Å), while in the molecule of the initial fervenulin the lengths of the bonds of the triazine ring are equal [5]. In the crystal structure of compound (IIa) the two active protons, HN4 and HN6, participate in the formation of intermolecular H-bonds: N4–H···O1 (x, 1/2−y, 1/2 + z) (N···O 2.99 Å) and possibly a bifurcate bond (H6–H···O1 (1−x, 1/2−y, 1/2−z), and N6–H···N5 (1−x, 1/2−y, 1/2−z) (N···O and N···N 2.99 and 3.02 Å, respectively), as a result of which planar networks are formed [from the H-bound molecules of compound (IIa)] parallel to the 011 plane.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of the compounds were recorded on a Bruker WP-200-SY instrument with a working frequency of 200 MHz. CSs were measured relative to TMS as internal standard. IR spectra were obtained on a UR-20 instrument in paraffin oil.

The x-ray structural investigation was carried out on a Syntex P1 four-circle diffractometer, λCuK_α, Ni filter, $\theta/2\theta$ scanning, $3° \leq 2\theta \leq 120°$. The crystals of compound (IIa), obtained by recrystallization from aqueous pyridine, were monoclinic: = 15.010(8), b =

*The numbering of the atoms of compound (IIa) used in the discussion of its structure and the values of the bond lengths and valence angles are given in Fig. 2. The coordinates of the atoms are given in Table 3.

8.344(6), c = 12.413(7) Å; β = 113.09(3)°; V = 1430(1) Å^3; z = 4; space group $P2_1/c$. The structure was interpreted by the direct method and was refined by the method of least squares in the full-matrix anisotropic approximation* to R = 0.091 (R_w = 0.100) for 1442 reflections.

Fervenulin (Ia) was obtained by the method of Ichiba et al. [6]. The synthesis of the 3-substituted fervenulin derivatives (Ic-f) is described in [4, 7].

6,8-Dimethyl-3-morpholino-5,6,7,8-tetrahydropyrimido[5,4-e][1,2,4]triazine-5,7-dione (Ib). A mixture of 0.1 g (0.44 mmole) of 3-chlorofervenulin [6], 5 ml of ethanol, and 0.1 g (1.15 mmole) of morpholine was boiled for 3-5 min. The reaction mixture was cooled and the precipitate of (Ib) was filtered off and recrystallized from ethanol. Yield 55-60%. mp 181-182°C. Found, %: C 47.6, H 5.0, N 30.3. $C_{11}H_{14}N_6O_3$. Calculated, %: C 47.5, H 5.0, N 30.2.

The synthesis of the 3-substituted 4a-(indol-3-yl)-6,8-dimethyl-2,4a,5,6,7,8-hexahydropyrimido[5,4-e][1,2,4]triazine-5,7-diones (IIa, c-e) has been described in [4].

4a-(Indol-3-yl)-6,8-dimethyl-3-morpholino-2,4a,5,6,7,8-hexahydropyrimido[5,4-e][1,2,4]-triazine-5,7-dione (IIb) was obtained in a similar way to (IIa). The yield of (IIb) was 60-65%. mp 230-231°C (water). Found, %: C 57.7, H 5.1, N 24.3. $C_{19}H_{21}N_7O_3$. Calculated, %: C 57.7, H 5.3, N 24.8.

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*The positional and temperature parameters of the H atoms revealed by a difference synthesis were not refined (the H atoms of the C7 methyl group were not localized because of their rotational disorder).