# ›URINES, PYRIMIDINES, AND CONDENSED ›YSTEMS BASED ON THESE COMPOUNDS. 13.* TRANSFORMATION OF FERVENULIN-1-OXIDE TO 8-ALKYLAMINOTHEOPHYLLINES UNDER THE ACTION OF ALKYLAMINES

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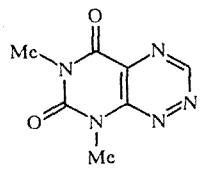
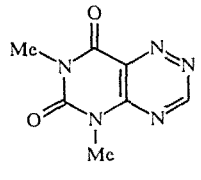
*Fervenulin-1-oxide undergoes reactions with secondary alkylamines in which the triazine ring is ruptured and 8-alkylaminotheophyllines are formed. The final product of the interaction of fervenulin-1-oxide with primary amines or with liquid ammonia is 1,3-dimethyl-5-imino-6-hydroximinouracil.*

The antibiotic fervenulin I, its isomer II, and their derivatives may interact with nucleophiles in several different ways: a) rupture of the uracil ring [2, 3] or the triazine ring [4, 5]; b) nucleophilic addition at the $C_{(4a)}$ and $C_{(8a)}$ atoms [6]; c) replacement of the hydrogen atom [3] or other atoms or groups [7, 8]. In the example of fervenulin-1-oxide (III), we have found still another type of interaction, a mixed interaction that includes addition of a nucleophile at the $C_{(3)}$–N bond and subsequent transformation of the triazine ring into an imidazole ring.



I



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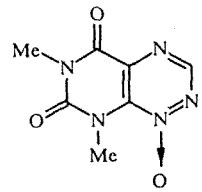

III

In the interaction of compound III with excess secondary alkylamines at a temperature from −70° to +40°C (depending on the boiling point of the amine), we unexpectedly recovered 8-alkylaminotheophyllines VI with yields of 7-20%. In this interaction, the reaction mixture heated up, gas bubbles were evolved, and the reaction was completed in 2-3 min (or 2 h, in the case of dimethylamine).

The structure of the compounds VI was established by spectroscopic methods (see Table 1) and countersynthesis from 8-bromotheophylline (VII) and the corresponding amines.

The mechanism through which the N-oxide III is transformed into 8-alkylaminotheophyllines VI apparently includes a stage of formation of a covalent adduct IV, opening of the triazine ring, and subsequent recyclization of the intermediates V (see Scheme on the following page).

We were unsuccessful in attempts to increase the yield of the compounds VI or to find other reaction products by varying the temperature and holding time or by using acetone as the solvent. The conversion of fervenulin-1-oxide to 8-alkylaminotheophyllines is apparently accompanied by processes involving a greater degree of breakdown. This is indirectly evidenced by a result that we obtained in studying the reaction of the N-oxide III with primary amines and with liquid ammonia. The products of this interaction are unstable, decomposing even in the course of recrystallization and emitting a

*For Communication 12, see [1].

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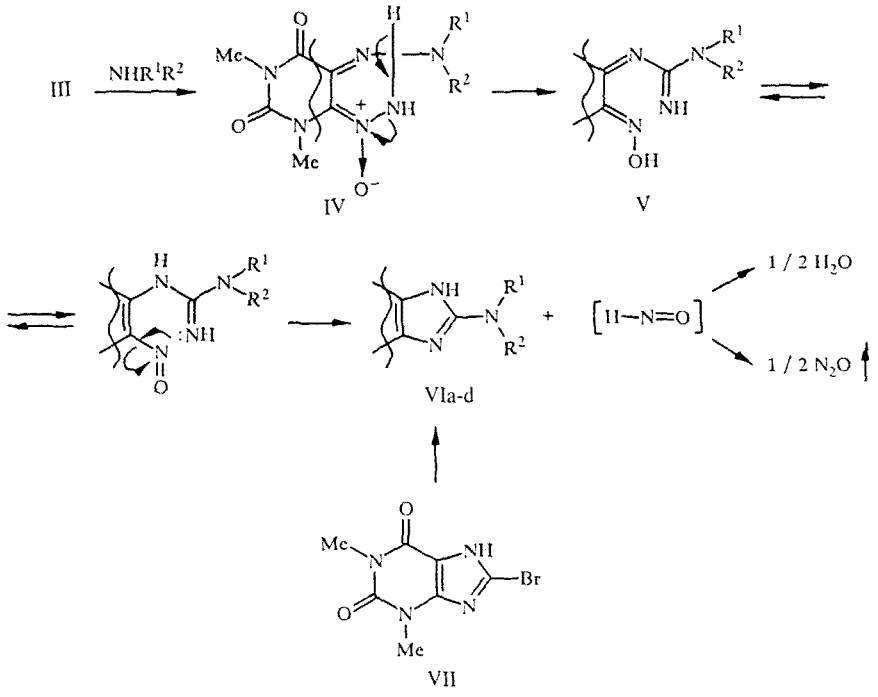
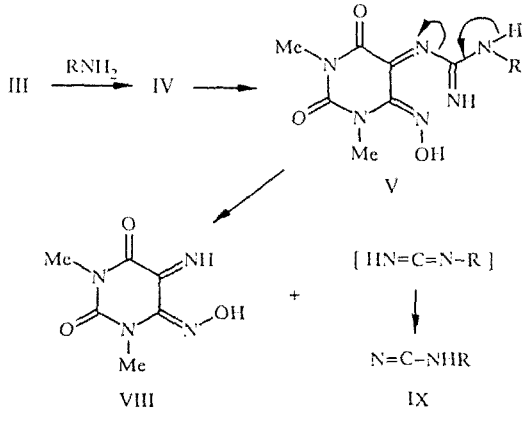


$NR^1R^2$: a) $NMe_2$, b) $NEt_2$, c) piperidino, d) morpholino

strong nitrile-like odor. These products are presumably uracils V containing two labile groupings – guanidino and oximino – and breaking down when heated to form compound VIII and cyanamides IX:



R = H, Me, Et, $PhCH_2$

Evidence supporting this view is provided by the IR spectra of the crude products from the reaction of the N-oxide III with liquid ammonia and primary amines, where we find two absorption bands that are characteristic for the N–H bond ($\nu$ 3150-3170 and 3350-3370 $cm^{-1}$); further evidence is provided by the PMR spectra, where we find signals of alkylamino group protons. In the EI mass spectra of these products, there are no peaks of the molecular ions, but fragment ions are registered, the principal signals of which can be explained by the following fragmentation scheme in the example of the adduct with benzylamine:

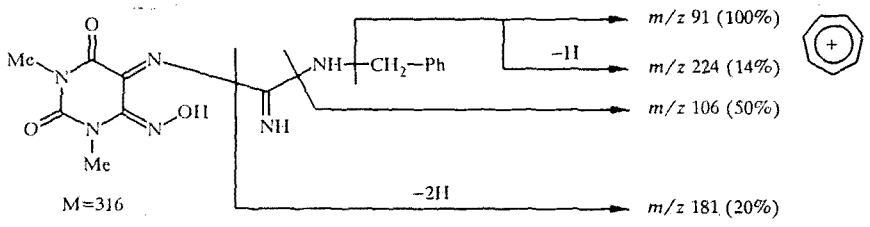


TABLE 1. Physicochemical Characteristics of Synthesized Compounds

| Compound | IR spectrum (white mineral oil), $\nu$, $cm^{-1}$ | PMR spectrum (DMSO-$d_6$),* $\delta$, ppm | $^{13}C$ NMR spectrum (DMSO-$d_6$), $\delta$, ppm | Mass spectrum,† m/z (and I, %), amu |
|---|---|---|---|---|
| III | 1670, 1703 (C=O), 3100 (C—H arom.) | 3,22 (3H, s, $N_{(8)}$—$CH_3$), 3,30 (3H, s, $N_{(6)}$—$CH_3$), 9,10 (1H, s, 3-H) | — | 209 (65) $M^+$, 181 (55) $[M - N—CH_2]^+$, 178 (13), 165 (37) $[M - N_2O]^+$, 152 (12), 142 (24), 137 (50) $[M - N_2O—NCH_2]^+$, 136 (20), 124 (31), 123 (17) |
| VIa | 1657, 1705 (C=O), 3186 (N—H), 2900...3400 (ass. NH) | 3,20 (6H, s, 2N—$CH_3$), 3,43 (6H, s, 2N—$CH_3$), 11,30 (s, NH) | — | — |
| VIb | 1665, 1703 (C=O), 3161 (N—H), 2900...3400 (ass. NH) | 1,13 (6H, m, $J$ = 7,5 Hz, $N(CH_2\underline{C}H_3)_2$), 3,19 (3H, s, $N_{(3)}$—$CH_3$), 3,35 (3H, s, $N_{(1)}$—$CH_3$), 3,38 (4H, q, $J$ = 7,5 Hz, $N(\underline{C}H_2CH_3)_2$), 11,34 (s, NH) | — | — |
| VIc | 1665, 1700 (C=O), 3147 (N—H), 2900...3400 (ass. NH) | 2,04 (6H, pseudosinglet, $\beta$- & $\gamma$-$CH_2$ piperidino), 3,36 (3H, s, $N_{(3)}$—$CH_3$), 3,66 (3H, s, $N_{(1)}$—$CH_3$), 3,68 (4H, m, $\alpha$-$CH_2$ piperidino), 11,56 (s, NH) | — | 263 (67) $M^+$, 262 (12) $[M - 1]^+$, 234 (14) $[M - NCH_3]^+$, 208 (12), 207 (12), 111 (14) |
| VId | 1660, 1701 (C=O), 3122 (N—H), 2900...3400 (ass. NH) | 3,33 (3H, s, $N_{(3)}$—$CH_3$), 3,60 (3H, s, $N_{(1)}$—$CH_3$), 3,78 (8H, pseudosinglet, morpholino), 11,60 (s, NH) | — | — |
| VIII | 1665, 1707 (C=O), 2900...3400 (ass. NH) | 3,21 (3H, s, $N_{(1)}$—$CH_3$), 3,42 (3H, s, $N_{(3)}$—$CH_3$), 3,5...5,5 (broad multiplet, NH & OH) | 27,93 (1-$CH_3$), 30,65 (3-$CH_3$), 123,33 (5-C), 148,65 (6-C), 150,91 (2-C), 156,04 (4-C) | — |

*Spectra of compounds VIc,d were taken in $CDCl_3$.

†Peaks with m/z ≤ 100 and I ≤ 10% are omitted.

In the IR spectrum of compound VIII, which was obtained by heating the primary reaction products, there are two absorption bands of C=O groups, indicating preservation of the uracil ring, and also a broad signal of an associated N–H bond in the 3100-3500 $cm^{-1}$ region. In the PMR spectrum of this substance in DMSO-$d_6$ there are only two singlets of N-methyl groups and a broad multiplet with $\delta$ 4-5.5 ppm. The $^{13}C$ NMR spectrum indicates the presence of six carbon atoms in the composition of the molecule of VIII, of which four atoms do not have any protons in their environment ($\delta$ 123.33, 148.65, 150.91, 156.04) and the other two are carbon atoms of methyl groups ($\delta$ 27.93 and 30.65 ppm).

Thus, the introduction of the N-oxide group into the heterosystem of fervenulin results in a much higher reactivity and a more complicated reaction.

## EXPERIMENTAL

IR spectra were registered on an IKS-40 instrument in white mineral oil. PMR spectra were registered on an XL-100 Varian instrument (working frequency 100 MHz, internal standard HMDS, for compounds III and VIc,d), a Bruker WH instrument (90 MHz, TMS, for compounds VIa,b), and a Unity-300 instrument (300 MHz, for compound VIII). $^{13}C$ NMR spectra were taken on a Unity-300 instrument (300 MHz). Mass spectra were obtained on a Varian MAT-311 A spectrometer with direct introduction of the sample into the ion source (accelerating voltage 70 eV, cathode emission current 1.0 mA).

Melting points were determined in a PTP instrument, in a sealed capillary. The chromatography was performed with the use of $Al_2O_3$, Brockman activity IV.

The physicochemical characteristics of the synthesized compounds are listed in Table 1.

Elemental analyses for C, H, and N matched the corresponding calculated values for these compounds.

**Fervenulin-1-oxide (III, $C_7H_7N_5O_3$).** A synthesis of compound III was described in [9]. In the procedure described below, the temperature and reaction time schedule have been modified in the interest of increasing the yield of the desired product.

A mixture of 4 g (20 mmoles) of fervenulin, 4 ml of trifluoroacetic acid, and 2.4 ml of 85% hydrogen peroxide was stirred for 6 h at 50°C. In the course of heating, an additional 1.4 ml of 85% $H_2O_2$ was added periodically. At the end of this time, the reaction mixture was poured into a porcelain dish and evaporated to dryness. The residue was recrystallized from ethanol. Yield 3 g (72%), lemon-yellow crystals, mp 165-166°C, in agreement with the data of [9].

**8-Dimethylaminotheophylline (VIa, $C_9H_{13}N_5O_2$).** ***A.*** A suspension of 0.4 g (2 mmoles) of compound III in 50 ml of dimethylamine was stirred for 2 h at −70°C, after which the reaction mixture was evaporated to dryness. The residue was treated with 3-5 ml of water, and the precipitate was filtered off and washed with cold ethanol and ether. The product was recrystallized from aqueous ethanol with a yield of 30 mg (7%); colorless needles, mp 319-321°C (decomp.); according to [10], mp 321-323°C (decomp.).

***B.*** A mixture of 0.2 g (0.7 mmole) of 8-bromotheophylline, 1 ml of dimethylamine, and 2 ml of dimethylformamide was refluxed for 1 h. After cooling, the white precipitate was filtered off and washed with a small quantity of hot water, ammonia solution, and water, and then air-dried. Yield 0.13 g (76%); colorless needles, mp 321-323°C (from glacial acetic acid; decomp.).

Samples of the compounds prepared by methods A and B gave identical IR spectra, and there was no depression of melting point for a mixed sample.

**8-Diethylaminotheophylline (VIb, $C_{11}H_{17}N_5O_2$).** ***A.*** A mixture of 0.4 g (2 mmoles) of compound III and 29 ml of diethylamine was heated cautiously to 40°C. The resulting orange-colored solution was poured into a porcelain dish and evaporated to dryness. The viscous residue was treated with 5 ml of hot water; after cooling, the precipitate was filtered off and recrystallized from hot ethanol. Yield 45 mg (9%); colorless needles, mp 253-255°C (decomp.); according to [11], mp 254-256°C (decomp.).

***B.*** A mixture of 0.1 g (0.4 mmole) of 8-bromotheophylline and 5 ml of diethylamine was refluxed for 3 h. The resulting solution was evaporated to dryness, and the residue was recrystallized from aqueous ethanol. Yield 60 mg (63%); colorless needles, mp 254-256°C (decomp.).

Samples of the compounds obtained by methods A and B gave identical IR spectra, and there was no depression of melting point for a mixed sample.

***C.*** A mixture of 0.2 g (1 mmole) of compound III, 33 ml of acetone, and 5 ml of diethylamine was held for 22 h at 20°C. The resulting orange-colored solution was evaporated to dryness; the residue was dissolved in 10 ml of chloroform and passed through a column with $Al_2O_3$ and eluted with chloroform. A light-yellow fraction with $R_f$ 0.3 was segregated. Yield 40 mg (16%); colorless needles, mp 256°C (from aqueous ethanol, decomp.). There was no depression of melting point for a mixed sample containing this material and that obtained by method A.

**8-Piperidinotheophylline (VIc, $C_{12}H_{17}N_5O_2$).** ***A.*** In a porcelain dish, 0.1 g (0.5 mmole) of compound III was mixed with 2 ml of piperidine. The resulting bright-yellow solution was rapidly evaporated to dryness. The residue was dissolved in 10 ml of chloroform and passed through a column with $Al_2O_3$ and eluted with chloroform. A light-yellow fraction with $R_f$ 0.5 was segregated. Yield 25 mg (20%); colorless needles, mp 295-296°C (from aqueous ethanol, decomp.).

***B.*** A mixture of 0.2 g (0.7 mmole) of 8-bromotheophylline and 4 ml of piperidine was refluxed for 2 h, and the resulting solution was evaporated. The residue was treated with 3-5 ml of water, and the precipitate was filtered off. Yield 0.2 g (98%); colorless needles, mp 296-297°C (from aqueous ethanol, decomp.).

Samples of the compounds obtained by methods A and B gave identical IR spectra, and there was no depression of melting point for a mixed sample.

**8-Morpholinotheophylline (VId, $C_{11}H_{15}N_5O_3$).** This was obtained in the same manner as compound VIc. Yield by method A 20%, method B 67%; colorless needles, mp 320°C (from aqueous ethanol, decomp.). There was no depression of melting point for a mixed sample consisting of the materials obtained by methods A and B.

**1,3-Dimethyl-5-imino-6-hydroximinouracil (VIII, $C_6H_8N_4O_3$).** A suspension of 0.4 g (2 mmoles) of the N-oxide III in 40 ml of liquid ammonia (or methylamine) was stirred for 1 h at −70°C. Then the reaction mixture was evaporated to

dryness; the residue was dissolved in 8 ml of ethanol and refluxed for 2 h, after which the solution was evaporated to dryness. The residue was treated with 5 ml of chloroform, and the precipitate was filtered off. Yield 0.14 g (42%); colorless crystals, mp 246-248°C (from xylene).

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