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# AMINOMETHYLATED URACILS, THEIR SYNTHESIS AND ANTIINFLUENZAL ACTIVITY

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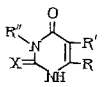
With the objective of seeking substances which have antitumor or antiviral properties, in the present work we have studied the aminomethylation reaction [1] of some uracil (I) derivatives, specifically 6-methyl-I (II), 6-methyl-2-thio-I (III), 5-methyl-I (thymine, IV), 5-hydroxymethyl-6-methyl-I (V), and 5-nitro-I (VI). Morpholine (VII), piperidine (VIII), and piperazine (IX) were used as the amines.

This reaction, based on I and III, has been previously studied by a number of workers [2-6]. However, the data which they obtained are contradictory. Thus, in [2, 6] it is indicated that the aminomethylation of I takes place at the N-3 and N-1 positions, while other workers [3-5] state that reaction occurs at the C-5 position.

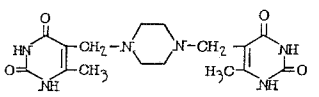
We have carried out the aminomethylation of II and III using formaldehyde and VII or VIII, taken in equimolar amounts or in excess, in an organic solvent medium (ethanol or methanol), at the boiling point of the reaction mixture.

Elemental analyses, UV and IR spectroscopy, and also some chemical reactions, show that the compounds which we obtained (IIa and b, and IIIa and b) are C-5 Mannich bases (the values of R, R', R", and X are given in Table 1).



IIa,b; IIIa,b
IVb; VIa, b

By boiling II with formaldehyde and an equivalent amount of IX in ethanol, N,N'-bis-(6-methyluracilmethylene-5)-piperazine (IId) was obtained:



Compounds IIa and b, and IIIa and b are titrated quantitatively with perchloric acid in the ratio 1:1 in anhydrous acetic acid in the presence of crystal violet as in indicator. The corresponding salts of IIa and b were isolated as a result of their reaction with solu-

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TABLE 1. C-5 and C-5,N-3-Aminomethylated Derivatives of Uracil and Their Salts

| Compound | R | R′ | R″ | X | Yield, % | Melting point, °C | Found, % | | | | Emperical formula | Calculated, % | | | | $R_f$ | | UV spectrum | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | N | S | Cl | citrate | | N | S | Cl | citrate | system A | system B | 0.1 N HCl | | methanol | | 0.1 N NaOH | |
| | | | | | | | | | | | | | | | | | | $\lambda_{max}$, nm | lg ε | $\lambda_{max}$, nm | lg ε | $\lambda_{max}$, nm | lg ε |
| IIa | $CH_3$ | Morpholino-methylene | H | O | 70,6 | 320—4 (with decomp.) | 18,52 | — | — | — | $C_{10}H_{15}N_3O_3$ | 18,66 | — | — | — | 0,36 | — | 263—264 | 3,89 | 265 | 4,20 | 282—285 | 3,82 |
| IIIa | $CH_3$ | Same | H | S | 75,5 | ~284 (with decomp.) | 17,60 | 13,60 | — | — | $C_{10}H_{15}N_3O_2S$ | 17,41 | 13,30 | — | — | 0,45 | 0,04 | 274—281 | 4,56 | 277—280 | 4,11 | 260 | 4,05 |
| IIb | $CH_3$ | Piperidino-methylene | H | O | 90,8 | ~330 (with decomp.) | 18,89 | — | — | — | $C_{11}H_{17}N_3O_2$ | 18,82 | — | — | — | 0,66 | 0,00 | 264 | 4,06 | 265 | 4,05 | 285 | 3,89 |
| IIIb | $CH_3$ | Same | H | S | 64,2 | 186—7 (with decomp.) | 16,32 | 12,23 | — | — | $C_{11}H_{19}N_3O_2S$ | 16,32 | 12,46 | — | — | 0,34 | 0,00 | 281—285 | 4,35 | 277 | 4,25 | 227—228<br>259—262<br>303—306 | 4,16<br>4,23<br>4,03 |
| IIc | $CH_3$ | Piperazino-methylene | Piperazino-methylene | O | 100,0 | ~280 (with decomp.) | 26,16 | — | — | — | $C_{15}H_{26}N_6O_2$ | 26,06 | — | — | — | 0,79 | 0,51 | 260—262 | 4,02 | 258—261 | — | 274—276 | 3,85 |
| IIIc | $CH_3$ | Same | Same | S | 93,1 | ~202 (with decomp.) | 24,86 | 8,52 | — | — | $C_{15}H_{26}N_6OS$ | 24,83 | 9,47 | — | — | 0,88 | — | 275 | 4,24 | 275—281 | 4,55 | 259—260 | 4,13 |
| VIa | H | $NO_2$ | Morpholino-methylene | O | 45,3 | 204—5 (with decomp.) | 21,61 | — | — | — | $C_9H_{12}N_4O_5$ | 21,87 | — | — | — | 0,93 | 0,65 | 230—234<br>290—298 | 4,58<br>4,63 | 234—236<br>259—261<br>337—338 | 3,81<br>3,80<br>4,23 | 240—241<br>350—366 | 4,23<br>4,51 |
| VIb | H | $NO_2$ | Piperidino-methylene | O | 51,1 | 199—200 (with decomp.) | 22,18 | — | — | — | $C_{10}H_{14}N_4O_4$ | 22,04 | — | — | — | 0,91 | 0,67 | 230—233<br>296—298 | 4,18<br>4,27 | 232—233<br>257—258<br>335—340 | 3,91<br>3,91<br>4,28 | 240—241<br>354—362 | 4,11<br>4,44 |
| IVb | H | $CH_3$ | Same | O | 85,8 | 176—186 | 18,72 | — | — | — | $C_{11}H_{17}N_3O_2$ | 18,82 | — | — | — | 0,73 | — | 263—265 | 4,13 | 263—265 | 4,29 | 283—286 | 3,70 |
| X | $CH_3$ | Morpholino-methylene | H | O | 71,1 | ~260—4 (with decomp.) | 16,15 | — | 13,88 | — | $C_{10}H_{15}N_3O_3 \cdot HCl$ | 16,06 | — | 13,55 | — | — | — | — | — | — | — | — | — |
| XI | $CH_3$ | Same | H | O | 36,0 | ~206—8 (with decomp.) | 9,70 | — | — | 33,90 | $C_{10}H_{15}N_3O_3 \cdot C_6H_8O_7$ | 10,06 | — | — | 34,28 | — | — | — | — | — | — | — | — |
| XII | $CH_3$ | Piperidino-methylene | H | O | 41,2 | ~232—4 (with decomp.) | 15,92 | — | 13,39 | — | $C_{11}H_{17}N_3O_2 \cdot HCl$ | 16,18 | — | 13,65 | — | — | — | — | — | — | — | — | — |
| XIII | $CH_3$ | Piperazino-methylene | Piperazino-methylene | O | 38,5 | ~96—101 (with decomp.) | 18,22 | — | 30,50 | — | $C_{15}H_{26}N_6O_2 \cdot 4HCl$ | 17,94 | — | 30,28 | — | — | — | — | — | — | — | — | — |
| XIV | $CH_3$ | Same | Same | S | 89,9 | ~158 (with decomp.) | 19,68 | 7,00 | 32,24 | — | $C_{15}H_{26}N_6OS \cdot 4HCl$ | 19,48 | 7,43 | 32,87 | — | — | — | — | — | — | — | — | — |

Note. Compounds IIa and b and IIIa and b were crystallized from a mixture of ethanol and water (2:1); X-XIV, from an acetone—water mixture (4:1); VIa and b, from methanol; IVb, from ethanol.

tions of hydrochloric or citric acid (Table 1). Compound IIa proved to be resistant to the action of hydrochloric acid (1:1), not only in the cold, but also on prolonged boiling (5h). The product isolated proved to be the hydrochloride of IIa (X).

On boiling V with formaldehyde and VIII in ethanol, and also on boiling V with VIII without formaldehyde, the very same product was obtained, identical with IIb. The individuality and identity of this compound was confirmed by evidence from thin-layer chromatography ($R_f$ 0.66; for the starting V and II, $R_f$ = 0.83 and 0.85, respectively), and from the UV and IR absorption spectra.

The aminomethylation of VI was carried out in ethanol at room temperature; and that of IV, at the boiling point of the reaction mixture. In both cases the N-3-aminomethylated derivatives were obtained — VIa and b, and VIb (values of R, R', and R'' are given in Table 1).

The C-5, N-3-dipiperazinomethylene derivatives of II and III (IIc, IIIc) were obtained on reaction of the latter with formaldehyde and excess IX in ethanol at room temperature. With hydrochloric acid they form the corresponding tetrahydrochlorides (XIII, XIV; Table 1).

It is well known that, on transition from an acid to neutral or alkaline media, the N-1-substituted pyrimidine bases do not give a bathochromic shift in the absorption maximum [7].

The UV absorption spectrum of the starting II in methanol is characterized by two high-intensity absorption maxima — below 220 nm and at 260 nm. They correspond to the absorption of the unsubstituted uracil in alcohol (202 and 259 nm), and are due to $\pi \rightarrow \pi^*$ electronic transitions, as the authors of [8] state. In 0.1 N hydrochloric acid (pH 1.1), the second maximum is hardly changed, but in 0.1 N sodium hydroxide (pH 12.2), it is shifted bathochromically to 270-276 nm.

The UV absorption spectra of the C-5-aminomethylated derivatives of II in methanol, like that of the starting II, are also characterized by two high-intensity absorption maxima (Table 1), which hardly change at pH 1.1, but are bathochromically shifted to 282-285 nm at pH 12.2.

A bathochromic shift of the absorption maximum in methanol by 5 nm in the second band as compared with the starting II is caused by an electron-donor group R' in the 5-position; an analogous bathochromic shift is observed in the thymine (206 and 265 nm) [8].

In methanol the starting III is also characterized by two high-intensity absorption maxima — below 220 nm and at 277-278 nm, which are also hardly changed at pH 1.1, but at pH 12.2 the second maximum is shifted hypsochromically to 259-260 nm, which is connected, apparently, with enolization of the compound in alkaline medium, as in the case of 2-mercapto-6-methylbenzothiazole [9] and the like.

The UV absorption spectra of the C-5 aminomethylated derivatives of III differ markedly from the spectra of the derivatives of II, and remind one of the absorption spectrum of the starting III. In methanol solution they are characterized also by two absorption maxima (Table 1); however, the second maximum is slightly shifted bathochromically at pH 1.1, and is shifted hypsochromically to 260 nm at pH 12.2; that is, the same thing is observed as in the case of the starting III. Compound IIIb is an exception; at pH 12.2 it is characterized by four absorption maxima. The absorption of the aminomethylated derivatives of II and III in the UV region can serve as one of the proofs of their structure as C-5-, and not N-substituted Mannich bases. The UV absorption spectra of the N-3-substituted Mannich bases from 5-nitrouracil (VIa and b) in methanol are characterized by three high-intensity absorption maxima (Table 1). The C-5, N-3 dipiperazinomethylene derivative of 6-methyluracil, IIc, in methanol is characterized by only two high-intensity absorption maxima, which are essentially not changed in acid medium, but are shifted bathochromically to 274-276 nm in alkaline medium. Two absorption maxima are also characteristic of the thio-analog, IIIc; the longer wavelength maximum is not changed in acid medium and is shifted hypsochromically in alkaline medium.

In the IR spectrum of IIa and IIb, complex broad bands are observed, with very intense maxima at 3195, 2945, 3243, and 2942 $cm^{-1}$, respectively, which corresponds to the stretching vibrations of the NH-groups [10, 11]. It was ascertained [10] that the lower of the frequencies corresponds to the stretching vibration of the N-3 N—H bond. In the absorption region of multiple bonds there are two intense bands with the frequencies 1750 and 1655 $cm^{-1}$ for IIa, and 1749 and 1655 $cm^{-1}$ for IIb. The authors of [10, 11] assign the highest frequencies to the C-2 C=O frequency and the lower ones to the C-4 C=O frequency. The presence of NH and C=O stretching vibration frequencies in these compounds confirms their structure as C-5 Mannich bases in the amide form. The detection of absorption frequencies for these compounds

at 1450 $cm^{-1}$ and at 1455 $cm^{-1}$, respectively, caused by vibrations of the $-CH_2-C^5=C^6-$ group [12], which is characteristic of C-5 aminomethylated uracils, is a confirmation of this conclusion. This frequency is absent in the starting II and III.

## EXPERIMENTAL (BIOLOGICAL)

The study of the virus-inhibiting activity of the synthesized compounds was carried out on a culture of cells of chicken fibroblasts with respect to virus of A/WSN influenza and in growing chicken embryos infected with A/WSN virus or A/Angila/42/72 (H3N2) virus. The infective activity of the influenza virus was 5.5 log $TCD_{50}$ for the cell culture and 6-7 log $EID_{50}$. The substances being studied, in nontoxic concentrations (1/4 to 1/8 of the maximum tolerable dose) were introduced into the studied biosystem 30 to 60 min after infection with the virus in a dose which caused a 100% effect of infection of the indicated models. Incubation of the virus-reproducing system was carried out at 37°C for 48 h. Effectiveness of antiinfluenzal action was evaluated from the degree of inhibition of virus reproduction in the biological systems studied.

## RESULTS AND DISCUSSION

As a result of the study of the virus-inhibiting activity of the aminomethylated uracils, compounds were found which were able to suppress the synthesis of hemagglutinins *in vitro*. This concerns the aminomethylated derivatives of VI, VIa and b. The compounds named depress the reproduction of A/WSN influenza virus with respect to hemagglutinin titer by 3-5 $\log_2$ units. The aminomethylated derivatives of II and III, and also the starting II, III, and VI, did not exert an appreciable effect on the reproduction of A/WSN virus in a cell culture.

Starting with the assumption that the synthesized compounds may exert an effect both on the course and outcome of an infection, and also on the reproducing system, it was fundamental to test them with respect to influenza virus *in ovo*, since such studies have not been conducted previously.

Analysis of the results obtained was carried out in a comparative aspect with I, which was used as a control as a starting product of the studied class of compound, and with remantadin (XV), a known anti-influenzal preparation. The activity of XV under the experimental conditions was not very strongly expressed, and was inferior to that of the derivatives IIa and b, and IId (Table 2). This was particularly marked with respect to A/Anglia/42/72 (H3N2) virus, where IIb and IId exceed the effectiveness of XV. As concerns I, its action is analogous in direction to the action of XV in experiments *in ovo*, however, the synthesized preparations IIa, b, and d gave a more pronounced effect and deserve a detailed study. It is to be noted that in experiments *in vitro* I caused a slight inhibition, while XV ensured a chemotherapeutic effect. However, in experiments *in ovo*, their action relative to the influenza virus is similar.

The results obtained allow one to conclude that it is advisable to carry out further directed syntheses and further search for antiviral compounds among the aminomethylated uracils.

## EXPERIMENTAL (CHEMICAL)

Chromatographic mobility was determined in a thin layer of sorbent on Silufol UV-254 plates, in the solvent systems acetone—15% trichloroacetic acid 65:35 (A); cyclohexanol saturated with water (B). The substances were dissolved in 50% methanol. The spots were developed with the aid of an FMT chromatoscope.

UV absorption spectra were taken on an SF-4 spectrophotometer, in methanol, in 0.1 N hydrochloric acid (pH 1.1), and in 0.1 N sodium hydroxide (pH 12.2).

IR spectra were taken on a UR-20 spectrophotometer, in potassium bromide disks (in the 1100-3400 $cm^{-1}$ region).

General Method of Preparing C-5-morpholinomethylene- and C-5-piperidinomethylene-6-methyluracils (IIa and b; IIIa and b). To a boiling solution of 0.01 mole of II or III in 30 ml of ethanol was added 0.02-0.05 mole of morpholine or piperidine and 2 ml of a 36% formaldehyde solution. The reaction mixture was boiled for 3 h, allowed to stand at room temperature for 24 h, and the precipitate which separated was filtered off and purified by crystallization (Table 1).

TABLE 2. Antiinfluenzal Activity of Aminomethylated Uracils in Experiments *in vitro* and *in ovo* with Respect to Influenza Virus

| Compound | Degree of inhibition of virus reproduction | | | | | |
|---|---|---|---|---|---|---|
| | in cell culture | | in growing chicken embryos | | | |
| | A/WSN | | A/WSN | | A/Anglia/42/72 (H3N2) | |
| | difference in hemagglutinin titers, units | P | difference in hemagglutinin titers, $\log_2$ units * | P | difference in hemagglutinin titers, $\log_2$ units * | P |
| II | 1,5 | <0,5 | 3,0 | >0,05 | 3,2 | >0,01 |
| IIa | 3,0 | >0,05 | 4,1 | <0,001 | 3,0 | >0,01 |
| IIb | 3,0 | >0,05 | 5,05 | <0,001 | 4,2 | <0,001 |
| IIc | 2,0 | >0,05 | 3,2 | >0,01 | 1,7 | <0,1 |
| IId | 1,7 | >0,2 | 4,0 | <0,001 | 4,6 | <0,001 |
| III | 0 | — | 1,2 | <0,5 | 2,0 | >0,05 |
| IIIa | 2,0 | >0,05 | 0,6 | >0,5 | 0,7 | >0,5 |
| IIIb | 2,0 | >0,05 | 1,65 | <0,5 | 1,0 | <0,5 |
| VI | 1,20 | >0,1 | 1,94 | >0,05 | 0 | — |
| VIa | 4,00 | <0,001 | 2,0 | >0,05 | 0 | — |
| VIb | 5,00 | <0,001 | 3,63 | >0,01 | 2,0 | >0,05 |
| Uracil | 2,0 | >0,05 | 3,3 | >0,01 | 2,2 | >0,05 |
| Remantadin | 4,0 | <0,001 | 3,5 | >0,01 | 1,1 | <0,5 |

*The difference between the mean geometric hemagglutinin titers as compared with the control in $\log_2$ units.

Note. P is the reliability of the difference between the $\log_2$ figures for the mean geometric titers in the experiment and in the control.

Infrared frequencies of IIa: 3195, 2945, 1750, 1655, and 1450 $cm^{-1}$; of IIb, 3243, 2942, 1740, 1655, and 1455 $cm^{-1}$.

Compound IIb was prepared similarly from 1.56 g (0.01 mole) of V, 2 ml of 36% formaldehyde solution, and 4.25 g (0.05 mole) of piperidine; yield, 1.70 g (76.2%), and also from 1.56 g (0.01 mole) of V and 4.25 g (0.05 mole) of piperidine, the yield of IIb was 1.45 g (65.0%). Infrared frequencies: 3250, 2940, 1753, 1662, and 1455 $cm^{-1}$.

Similarly were prepared N-3 piperidinomethylene-5-methyluracil (IVb), and, starting from equivalent amounts of the starting materials, N,N'-bis-(6-methyluracilmethylene-5)-piperazine (IId). The yield was 55.2%, m.p. about 178°C (with decomposition). $R_f$ 0.53 (system B). Found, N 23.54; calculated for $C_{16}H_{22}N_6O_4$, N 23.19. UV spectrum: $\lambda_{max}$, nm (log ε): at pH 1.1, 259-265 (4.66); in methanol, 259-263 (4.27); at pH 12.2, 279-280 (4.20).

General Method of Preparing C-5, N-3 Dipiperazinomethylene-6-methyluracils (IIc, IIIc). To a solution of 0.025 mole of piperazine hexahydrate in 15 ml of ethanol was added 0.01 mole of II or III and 2 ml of 36% formaldehyde solution; a precipitate separated quantitatively at once, it was kept for 24 h, and the separated precipitate was washed with organic solvents.

General Method of Preparing N-3-morpholino- or N-3-piperidinomethylene-5-nitrouracil (IVa and b). Compound VI (0.01 mole) was dissolved in 50 ml of methanol with heating in the presence of 0.05 mole of morpholine or piperidine, and 2 ml of 36% formaldehyde solution was added. The mixture was allowed to stand at room temperature for 48 h. The precipitate which separated was filtered off and purified by crystallization.

The hydrochlorides and citrates of the C-5-morpholino-, C-5-piperidinomethylene-6-methyluracils, and C-5,N-3-dipiperizinomethylene-6-methyluracils (X-XIV) were prepared by the method of [13].

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# METHOD FOR SELECTING TOPOLOGICAL AND TOPOGRAPHICAL DESCRIPTORS OF THE BIOLOGICAL ACTIVITY OF CHEMICAL COMPOUNDS

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One of the most promising areas for the application of computer methods of drug design [1] is the generation of new series of active compounds ("lead generation") [2]. This is based on the identification of similarities between compounds of different chemical series displaying the same type of activity. Here we describe a method for representing the structures of compounds and an algorithm based on the structural approach to carry out this function.

On the basis of a logical analysis of compound descriptions this algorithm selects the substructures common to compounds of the different chemical series that are responsible for the particular activity — the topological or topographical descriptions of the activity. The topographical descriptors take account of the steric structure while the topological descriptors are some fragments of the structural formula of the compound.

However, the representation of molecules in the form of structural formulas is unnecessarily detailed and laborious for the purpose of finding general structure–activity correlations. Important structural information can be retained while the work of finding the topological descriptors is greatly reduced by going from the simple chemical graph — the structural formula of the compound — to the aggregated graph of the descriptor centers [1]. The structures of the compounds can then be described by the matrices of the descriptor centers (MDC). This sort of structural representation is a development of the fragment code of substructure superposition [3]. The diagonal elements of the MDC contain the codes of the descriptor centers — the potentially active centers of the molecule, which include all the heteroatoms and the aromatic systems as a whole. The element of the MDC in the i-th row and the j-th column contains the shortest distance between the i-th and the j-th descriptor centers in terms of the number of atom–atom bonds. We can exemplify this coding with acetophenothiazine and hydroxyzine; their MDC's are given on the next page.

In these MDC's the codes of the descriptor centers are: 03 tertiary nitrogen atom, 11 OH group, 12 ether oxygen, 22 sulfur, 31 chlorine, 33 benzene, and 41 terminal $CH_3$ group. We give only half of each of the matrices, since they are symmetrical about the main diagonal.

The basis of the algorithm for identifying the structural (topological or topographical) descriptors of the activity is a special procedure for comparing two matrices, which can be used to find the submatrices common to these compounds. These submatrices and the corresponding structural fragments for our example are:

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