# STUDIES ON THE SERIES OF AZOLES AND AZINES.

# 66.* SYNTHESIS, SPECTRA AND STRUCTURE OF 5-ARYLAZO- AND 5-ARYLIDENEAMINO-2,4,6-TRIAMINOPYRIMIDINES AND THEIR 6-HYDROXY ANALOGS

Zh. V. Belodedova, N. A. Smorygo, V. S. Mirzoyan, R. G. Melik-Orandzhanyan, E. P. Studentsov, and B. A. Ivin

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5-Arylazo and 5-arylideneamino-2,4,6-triaminopyrimidines and their 6-hydroxy analogs were obtained by azo coupling of 2,4,6-triamino- and 2,4-diamino-6-hydroxypyrimidines with aryldiazonium salts, and also by the reaction of benzaldehydes with 2,4,5,6-tetraamino- and 2,4,5-triamino-6-hydroxypyrimidines, respectively. According to spectral data, in solvents with different polarity, these compounds exist preferentially in the triamino- or diaminohydroxy form. The main paths of the mass spectrometric fragmentation of the compounds studied have been determined.

Up to the present time, quite a large number of investigations have already been carried out, dealing with the search for the potentially antitumorigenic agents among Schiff bases [2-5]. Among the folic acid antagonists studied, there are not only preparations which fairly accurately copy its structure, but also compounds in which only the pyrimidine ring has been retained that ensures a coupling with apoenzyme, and a group that ensures hydrophobic coupling. Among the inhibitors, attention had been paid to certain derivatives of 5-aryl-, 5-benzyl-, 6-aza-, and 6-substituted 5-arylazo-2,4-diaminopyrimidines, and the relationships between the changes in their biological activity and in their structure have been qualitatively examined [6, 7]. In several papers, a quantitative "structure–activity" relationship of the antifolates has been established [8]. The high inhibiting activity of certain 5-arylazopyrimidines [9-11] indicates that the enzymically coupled inhibitor has a configuration similar to that of folic acid. Variation in substituents changes the distribution of the electron density, and thus influences the ability of the inhibitor to be coupled by either the formation of a charge-transfer complex or as the result of hydrophilic interactions.

We continued to search for potentially antitumorigenic compounds and to study the relationship between the structure and the biological effects of the compounds being investigated, and turned our attention to the synthesis of a series of pyrimidine Schiff bases and their azo analogs, the arylazopyrimidines. For this purpose, we used the reaction of 2,4,6-triamino- and 2,4-diamino-6-hydroxypyrimidines with diazotized amines [12], and synthesized two series of 5-arylazo-2,4-diaminopyrimidines (I, II). By condensing 2,4,5,6-tetraamino- and 2,4,6-triamino-4-hydroxypyrimidines with substituted benzaldehydes, two series of 2,4,6-triamino- and 2,4-diamino-6-hydroxy-5-arylideneaminopyrimidines (III, IV) respectively, were obtained.

In the mass spectra of all the arylazopyrimidines and arylideneaminopyrimidines (I-VI) (Table 1, see scheme) the peaks of the molecular ions have maximal activity. In some cases, peaks of double-charged molecular ions are observed (compounds Ii, j; IVb-i). In contrast to the case of azomethines III and IV, the spectra of azo compounds I and II had no peaks of [M−1] and [M− 2]. It is possible that this is because the elimination of two hydrogen atoms from the molecular ion leads to the formation of stable 8-arylpurines or 8-aryloxazolopyrimidines ($A_2$, X = O, NH). Azo compounds I and II and their carbo analogs III and IV have only one common path

*See [1] for Communication 65.

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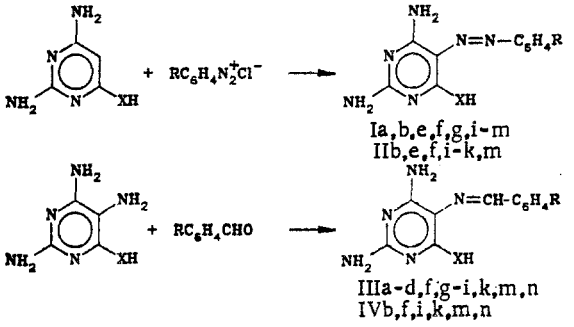
TABLE 1. Mass Spectra of 2,4,6-Triamino- and 2,4-Diamino-6-hydroxy-5-arylazo and 5-Arylideneaminopyrimidines (I-IV)

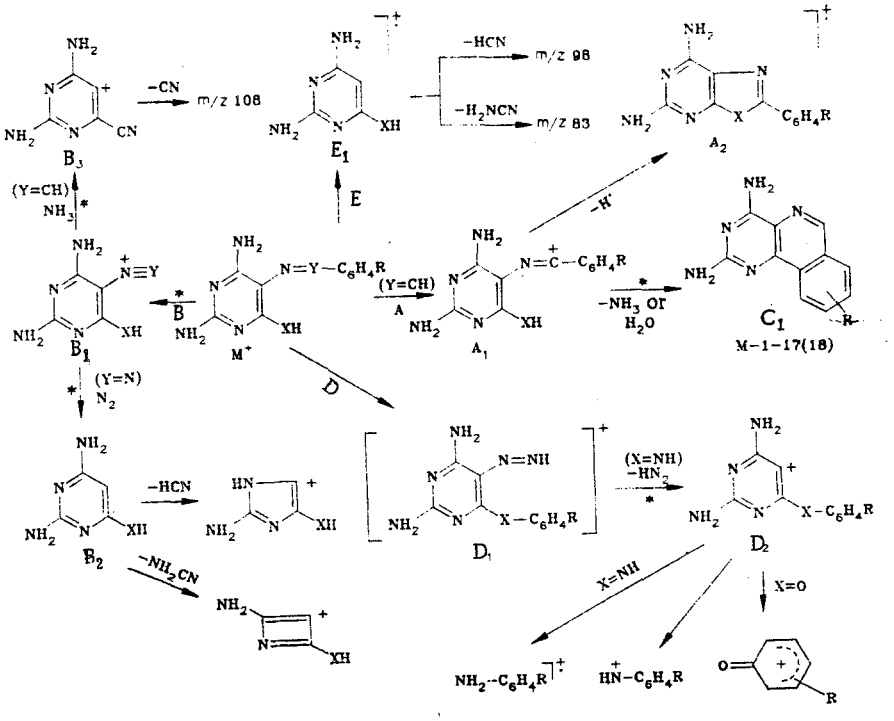
| Compound | M+ | Ions formed by main of fragmentation | | | | | | | | Other ions |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $A_1$ | $A_2$ | $B_1$ | $B_2$ | $B_3$ | $D_1$ | $D_2$ | $E_1$ | |
| Ia | 274 (100) | — | — | 152 (32) | 124 (55) | — | — | — | — | 244 (20), 82 (55) |
| Ib | 274 (100) | — | — | 152 (35) | 124 (54) | — | — | — | — | 244 (20), 82 (54), 73 (23) |
| If* | 263 (100) | — | — | 152 (36) | 124 (56) | — | — | 234 (12) | — | 266 (8), 265 (42), 111 (13), 82 (50) |
| Ii | 229 (100) | — | — | 152 (30) | 124 (42) | — | — | 200 (14) | — | 82 (36), 77 (8) |
| Ij | 243 (100) | — | — | 152 (29) | 124 (45) | — | — | 214 (21) | — | 91 (22), 82 (36) |
| Ik | 259 (100) | — | — | 152 (24) | 124 (36) | — | — | 230 (24) | — | 107 (22), 82 (30) |
| Iℓ | 259 (100) | — | — | 152 (38) | 124 (46) | — | — | 230 (6) | — | 151 (18), 123 (15), 82 (38), 77 (7) |
| IIi | 230 (100) | — | — | 153 (47) | 125 (16) | — | — | 201 (3) | — | 138 (30), 93 (46), 83 (8), 77 (8), 70 (14) |
| IIj | 244 (100) | — | — | 153 (32) | 125 (8) | — | — | 215 (4) | — | 138 (16), 107 (52), 106 (44), 91 (25), 78 (37), 70 (10), 63 (34) |
| IIIa | 273 (100) | 272 (22) | 271 (18) | 151 (22) | — | 134 (5) | 256 (5) | — | 125 (5) | 241 (22), 229 (44), 226 (18), 225 (7), 139 (27), 138 (53), 122 (8), 121 (22), 119 (22), 118 (15), 112 (23), 111 (22), 104 (11), 96 (44), 93 (22), 92 (12) |
| IIIb | 273 (100) | 272 (22) | 271 (17) | 151 (14) | — | 134 (4) | 256 (5) | — | 125 (6) | 241 (24), 229 (13), 226 (17), 139 (32), 138 (40), 121 (24), 119 (12), 118 (22), 112 (16), 111 (14), 96 (38), 93 (18), 92 (8), 60 (12) |
| IIIc | 273 (100) | 272 (18) | 271 (10) | 151 (50) | — | 134 (5) | — | — | 125 (22) | 243 (18), 241 (8) |
| IIIf* | 262 (100) | 261 (33) | 260 (42) | 151 (54) | — | 134 (5) | 245 (5) | — | 125 (32) | 265 (7), 264 (37), 98 (12) |
| IIIh | 244 (100) | 243 (21) | 242 (20) | 151 (30) | — | 134 (3) | — | — | 125 (18) | 98 (10), 71 (8) |
| IIIi | 228 (100) | 227 (28) | 226 (20) | 151 (50) | — | 134 (5) | — | — | 125 (25) | 98 (10) |
| IIIk | 258 (100) | 257 (35) | 256 (33) | 151 (32) | — | 134 (4) | 241 (10) | — | 125 (36) | 139 (10), 98 (10), 78 (28), 63 (20) |
| IVb | 274 (100) | 273 (26) | 272 (72) | 152 (27) | — | 135 (3) | 256 (5) | — | 126 (45) | 244 (14), 242 (27), 227 (8), 226 (18), 139 (14), 121 (10), 120 (12), 118 (21), 112 (8), 98 (22), 86 (12), 77 (5) |
| IVf* | 263 (100) | 262 (23) | 161 (18) | 152 (36) | — | 135 (3) | 245 (5) | — | 126 (72) | 266 (10), 265 (40), 99 (8), 98 (32), 78 (20), 63 (10) |
| IVi | 229 (100) | 228 (28) | 227 (22) | 152 (34) | — | 135 (3) | 211 (5) | — | 126 (44) | 98 (22) |
| IVk | 259 (100) | 258 (30) | 257 (20) | 152 (24) | — | 135 (6) | 241 (5) | — | 126 (43) | 98 (20) |

*For chlorine containing ions, their masses with $^{35}Cl$ isotope are given.

of fragmentation, path B, consisting in splitting of the aryl group and leading to the formation of ion $B_1$, $[M - C_6H_4R]$. The latter is formed directly from the molecular ion, as confirmed by a metastable transition, observed in all cases. Path B is the main path during fragmentation of arylazopyrimidines I and II, but this and two other paths (A, C) are equally probable for azomethines III and IV. Further fragmentation of ion $B_1$ proceeds with elimination of a nitrogen atom from $C_{(5)}$ during the fragmentation of azo compounds I and II, and a molecule of ammonia or water in the case of azomethines III and IV, due to splitting of an XH group at $C_{(6)}$ and hydrogen atom from the substituent at $C_{(5)}$. The last fragmentation of the $B_2$ and $B_3$ ions is characteristic of substituted 2,4-diaminopyrimidines [13].




I, III X=NH; II, IV X=O; I—IV a R=2-$NO_2$; b R=4-$NO_2$; c R=3-$NO_2$; d R=4-CHO; e R=4-$SO_3H$; f R=4-Cl; g R=4-I; h R=3-OH; i R=H; j R=4-Me; k R=4-OME; ℓ R=2-OMe; m R=4-$NMe_2$; n R=4-$NEt_2$




A distinct path of fragmentation of azo compounds I and II is the elimination of two nitrogen atoms and a hydrogen atom from the molecular ion (path D). In all cases, this is characterized by a metastable transition. This path of fragmentation is possible if we assume that the aryl migrates to group X and hydrogen to the exocyclic nitrogen atom at $C_{(5)}$, leading to a transformation of the molecular ion $M^+$ into form $D_1$. The formation of ion $D_2$ then becomes possible, in which the $C_{(6)}$–X bond is further split. A similar migration of the phenyl group was also observed during mass fragmentation of phenylpyrazolones [13].

A special feature of the mass spectrometric fragmentation of azomethines III and IV is the formation of ion $C_1$, which, as indicated by the corresponding metastable transition, is formed from the $[M - 1]^*$ ion by elimination of ammonia. Despite the low intensity of the peak of this ion, it is definitely interesting for azomethines III and IV.

TABLE 2. Ionization Constants, Distribution Coefficients p, UV and PMR Spectra of Compounds I, II

| Compound | $pK_a$ | lg p | UV spectrum (in ethanol) | | PMR spectrum, δ, ppm* |
|---|---|---|---|---|---|
| | | | $\lambda_{max}$, nm | $\varepsilon \cdot 10^{-3}$ | in DMSO-$D_6$ ($C_6H_4$) |
| Ia | — | — | 256, 420 | 13,7; 18,0 | 7,85—7,65 |
| Ib | −0,81<br>5,40 | 2,61 | 260, 444 | 12,4; 24,2 | 8,05; 8,25;<br>8,31; 8,40 |
| Ie | — | — | 246, 382 | 9,02; 18;5 | 7,70—8,10 |
| If | −0,62<br>5,05 | 2,73 | 254, 386 | 16,7; 25,4 | 7,45; 7,68;<br>7,85; 7,95 |
| Ig | — | — | 255, 390 | 15,8; 24,0 | 7,70; 7,80;<br>7,85; 7,95 |
| Ii | −0,58 | 2,70 | 252, 380 | 18,8; 25,6 | 7,55—8,10 |
| Ij | −0,69 | 2,71 | 255, 384 | 17,0; 21,2 | 7,10; 7,3;<br>7,60; 7,8 |
| Ik | −0,70 | 2,69 | 290, 380 | 11,8; 26,3 | 6,35; 7,10 |
| Iℓ | — | 2,59 | 255, 382 | 11,8; 20,3 | 7,12; 7,25;<br>7,40; 7,55 |
| Im | −1,17<br>4,20 | 3,05 | 270, 330, 442 | 17,0; 11,2; 22,6 | 6,60; 6,80;<br>7,50; 7,70 |
| IIb | — | 1,85 | 290, 410, 580 | 1,45; 24,4; 17,2 | — |
| IIe | — | — | 245, 384 | 10,9; 17,4 | — |
| IIf | — | — | 243, 380 | 11,4; 19,1 | — |
| IIi | — | 2,57 | 241, 374 | 2,8; 3,02 | — |
| IIj | — | 1,63 | 245, 384 | 10,9; 17,4 | 6,90—7,80 |
| IIk | — | 1,87 | 287, 364 | 14,8; 27,4 | — |
| IIm | — | 1,92 | 260, 320, 440 | 18,4; 7,7; 24,7 | — |

*Signals of R: δ 2.35 (Ij), 3.82 (Ik), 2.95 (Im), 3.90 ppm (Iℓ).

One of the main paths of fragmentation of azomethines III and IV is path E that includes the rupture of the $C_{(5)}$—N bond with migration of the hydrogen atom to the charged fragment. This path is more characteristic of the hydroxy derivatives IV, as indicated by the high peak intensity of the corresponding ions in their spectra. Ion $E_1$ thus formed decomposes further, possibly in accordance with known mechanisms [14, 15]. These assume that HCN is eliminated at the expense of the $C_{(4)}$—$NH_2$ group. This is possible only if ion $E_1$ exists in the imine form. For hydroxy derivatives IV, ion $E_1$ preferentially loses CO. In parallel with these two processes, elimination of the neutral $H_2NCN$ particle is observed in the two series of (III, IV).

In the case of mass spectra of nitro derivatives, besides the above processes, nitro and nitroso groups are eliminated, which is characteristic of the nitro compounds. It should be noted that the mass spectra of compounds IIIa, b differ from the spectrum of isomer IIIc in the absence of elimination of a nitroso group from the molecular ion. In the spectra of o- and p-nitro derivatives (IIIa, b), several intense peaks of ions with m/z 139, 138, 121, 112, 111, 119, 118, 96 are observed, but these are absent in the spectra of the isomer IIIc. It is possible that in this case, a hydrogen atom is split not only from the azomethine group, (formation of ions $A_1$), but also from the benzene ring, followed by its expansion and splitting.

Thus, the fragmentation of 5-arylazo-2,4,6-triaminopyrimidines and their 6-hydroxy analogs is very simple, and proceeds mainly along two paths: splitting of aryl and elimination of nitrogen and hydrogen with a simultaneous transfer of the aryl to nitrogen or oxygen at $C_{(6)}$. The mass spectrometric fragmentation of azomethines is much more complex, and includes at least three approximately equally probable paths, one of which (the elimination of aryl from the molecular ion) is the same as that indicated for the azo analogs. The molecular ions are very stable (the corresponding peaks in the spectra have maximal intensity) and decompose with rupture of the $C_{(5)}$=N bond or with splitting of the aryl. In no case was there a fragmentation of the pyrimidine ring at the first stages of the fragmentation. The substituent in the aryl has little influence on the direction and intensity of the fragmentation in all the series of compounds. Replacement of the carbon by nitrogen does not lead to a qualitative change in the fragmentation scheme, and only in the case of azomethines promotes rupture of the bond.

In the region of the stretching and deformational vibrations of the pyrimidine ring bonds, i.e., below 1600 $cm^{-1}$, the IR spectra of the crystalline samples of all the 5-arylazo-

TABLE 3. Data on UV and PMR Spectra of 6-Amino- and 6-Hydroxy-5-arylideneamino-2,4-diaminopyrimidines (III, IV)

| Compound | UV spectrum (in ethanol) | | PMR spectrum, δ, ppm (in DMSO-$d_6$)* | |
|---|---|---|---|---|
| | $\lambda_{max}$, nm | $\varepsilon \cdot 10^{-3}$ | N=CH | $C_6H_4$ |
| IIIa | 245, 390 | 12,8; 7,36 | — | — |
| IIIb | 267, 400 | 11,3; 5,81 | — | — |
| IIIc | 390 | 6,60 | 8,78 | 8,70—7,50 |
| IIId | 265, 420 | 37,7; 23,80 | 8,70 | 7,90; 8,25 |
| IIIf | 265, 382 | 14,0; 9,1 | 8,85 | 8,25; 8,10; 7,80; 7,65 |
| IIIg | 272, 366 | 1,8; 13,3 | 10,45 | 8,50; 8,35; 8,15; 8,00 |
| IIIh | 262, 374 | 15,0; 8,83 | 8,78 | 7,75—8,40 |
| IIIi | 262, 374 | 13,0; 9,92 | 8,65 | 7,45; 7,55; 7,85; 7,95 |
| IIIk | 286, 370 | 18,8; 97,5 | 8,85 | 7,20; 7,35; 8,05; 8,20 |
| IIIm | 245, 346 | 15,4; 24,9 | 8,95 | 7,25; 7,35; 8,15; 8,30 |
| IIIn | 245, 380 | 12,0; 27,1 | — | — |
| IVb | 265, 420, 382 | 14,7; 20,8; 19,3 | 8,82 | 8,0—8,4; 7,85; 7,70 |
| IVf | 240, 291, 382 | 13,5; 10,9; 19,3 | 10,10 | 8,30; 8,15; 7,85; 7,70 |
| IVi | 237, 290, 354 | 14,0; 10,5; 18,7 | 9,85 | 7,55; 7,65; 8,00; 8,05 |
| IVk | 245, 391 | 5,9; 14,3 | 9,80 | 7,0—7,8 |
| IVm | 350 | 44,6 | — | — |
| IVn | 245, 356 | 10,3; 19,2 | — | — |

*Signals of R: δ 10.15 (IIId), 3.45 (IIIm), 3.85 (IVk), OH signals: δ 10.3 (IVb), 10.90 (IVk).

and 5-arylideneamino-2,4,6-triaminopyrimidines (I, III), are similar to the spectra of 2,4,6-triaminopyrimidine [16], and differ only in the NH region. In the spectrum of 2,4,6-triaminopyrimidine only two frequencies $\nu_{as\,NH_3}$ 3430 $cm^{-1}$ and $\nu_{s\,NH_3}$ 3319 $cm^{-1}$ are observed which belong to the vibrations of three amino groups, while in the spectra of 5-substituted 2,4,6-triaminopyrimidines (I, III), four to five bands are noted (for example, for 5-benzylideneamino-2,4,6-triaminopyrimidine $\nu_{NH_2}$ 3590, 3500, 3465, 3390, and 3360 $cm^{-1}$). This increase in the number of bands is clearly due to a decrease in symmetry. In the spectra of 5-arylideneamino derivatives (III) there is a band in the region of 3160-3120 $cm^{-1}$, belonging to $\nu_{CH}$ of the exocyclic HC=N group.

In the IR spectra of 5-arylazo- and 5-arylideneamino-2,4-diamino-6-hydroxypyrimidines, four bands are observed in the 3300-3600 $cm^{-1}$ region, belonging to the $\nu_{as}$ and $\nu_s$ of two $NH_2$ groups, a band at 3150 $cm^{-1}$ ($\nu_{CH}$) and a broad $\nu_{OH}$ band in the 3200-2900 $cm^{-1}$ region. It is assumed [17] that in the crystalline state, 2,4-diamino-6-hydroxypyrimidines exist in the form of a mixture of two tautomeric forms, an enol and carbonyl one, although judging from the intensities of the $\nu_{C(6)=O}$ band at 1694 $cm^{-1}$, the fraction of the carbonyl form is small. In the spectra of 5-arylideneamino-2,4-diamino-6-hydroxypyrimidines (IV) bands are observed which belong to the vibrations of the $C_{(6)}$–OH fragment ($\nu_{C-O}$ ~ 1360 cm and $\delta_{OH}$ ~ 1100 $cm^{-1}$), and there is no absorption in the vicinity of 1700 $cm^{-1}$. In the spectra of 5-arylazo-2,4-diamino-6-hydroxypyrimidines, there is a medium intensity band around 1700 $cm^{-1}$, which can be assigned to the stretching vibrations of the $C_{(6)}$=O group. We can thus assume that 5-arylazo derivatives II exist in the crystalline state in form of a mixture of a carbonyl and enol forms. As expected, in the IR spectra of all the compounds studied, bands appear near 1600 $cm^{-1}$, corresponding to the $\nu_{C=C}$ vibrations of the aryl substituent, absorption bands of the stretching vibrations of the exocyclic C=N bond at ~1620 $cm^{-1}$ for 5-arylideneamino-2,4,6-triamino- and 2,4-diamino-6-hydroxypyrimidines (III, IV) and $\nu_{N=N}$ 1420 $cm^{-1}$ for 5-azo analogs (I, II). Thus, the IR spectra in the crystalline state show that only 2,4-diamino-6-hydroxy-5-arylazopyrimidines exist in the form of a mixture of two tautomeric forms, but in this case the hydroxy form predominates.

According to UV and PMR spectral data, arylazopyrimidines I, II (Table 2) and arylideneaminopyrimidines III, IV (Table 3) also exist preferentially in the form of hydroxy derivatives in alcohol and dimethyl sulfoxide solutions. In the UV spectra of alcoholic solutions

of all the arylazopyrimidines, as in the case of arylidineaminopyrimidines, two absorption maxima are observed; a short-wave maximum (245-290 nm) due to electronic transitions of the benzene and pyrimidine rings, and a long-wave one due to the electronic transitions in the conjugated system of bonds between the pyrimidine and benzene rings.

Up to the present, the behavior of these compounds in aqueous solutions has not been systematically studied. We therefore studied spectrophotometrically the acid-base properties and the stability of the compounds synthesized in aqueous solutions with different acidities. We found that all the 6-amino- and 6-hydroxy-2,4-diamino-5-arylazopyrimidines (I, II) are stable in aqueous solutions from $H_0$ = 6.86 to pH 11, as in alcoholic solutions.

It is known [18] that in alkaline media para-substituted 2,4-diamino-5-arylazo pyrimidines can form an anion in which the amino group at $C_{(6)}$ is readily replaced in aqueous solutions by a hydroxyl, and this leads to the disappearance of the isobestic points. The good reproducibility of the spectra and the presence of a pair of isobestic points for each band in all the cases that we studied indicated that if it takes place, the hydrolysis of compounds I and II is very slow, and the observed change in the spectrum relates to one type of transformation, namely to ionization. 2,4-Diamino-5-arylazopyrimidines I have two degrees of ionization. This is indicated by two pairs of isobestic points for each compound during a change in the spectra with change in the pH of the solutions from 3 to 11 and from pH 1.0 to $H_0$ = −6.8. It was thus possible to spectrophotometrically measure the ionization constants of 2,4,6-triamino-5-arylazopyrimidines (Ib, f, i-k, m) (Table 2).

To evaluate spectrophotometrically the changes in the lipophilicity of compounds I and II depending on the nature of the substituent, we determined the distribution coefficients in the octanol–water system (Table 2). The absence of a correlation between the experimentally determined values of log P and the aromatic Hantzsch π-constants was unexpected. It is possible that this is due to the specificity of the intra- and intermolecular interactions of the substituents with the pyrimidine ring, or due to specific solvation features of the compounds studied. There is no strict quantitative relationship between changes in the lipophilicity and the biological effect of the preparations, but the tendency of the activity to increase with increase in the hydrophilicity is very clear, and in the case of electron-donor substituents it is also regular in character. This probably indicates that the lipophilicity is not the only parameter responsible for the appearance of the biological action.

In contrast to 5-arylazopyrimidines I and II, 5-arylideneaminopyrimidines III and IV very rapidly change in aqueous solutions. The rate of the process depends also on the acidity of the medium and on the nature of the substituent in the benzene and pyrimidine rings. In all the cases studied at pH 1-7, the long-wave band that is observed in the UV spectra of the alcoholic solutions is not present in the spectra of solutions of azomethines II. In the spectra of alkaline solutions, this band is observed, but its intensity is very low. The transformations of arylideneaminopyrimidines in acid media are irreversible in character. According to TLC data, there is one new product in the solution, traces of benzaldehyde, but no initial compound. Hence it can be assumed that the spectra of acid solutions (pH < 7) of 5-arylideneaminopyrimidines correspond to the products of their transformations and not to pyrimidines proper. It should be noted that the spectral characteristics of these products are very close to those of the spectra of 8-substituted dihydropurines.

The changes in the electronic spectra of 5-arylideneamino-2,4-diamino-6-hydroxypyrimidines (IV) in aqueous solutions of acids and bases are similar to those observed for triamino derivatives III.

## EXPERIMENTAL

The mass spectra were run on a MX-1303 spectrometer with a direct introduction of the sample into the ionization region at the temperature of 150-180°C. The energy of the ionizing voltage was 30 eV, emission current 150 μA. The UV spectra were recorded on SF-20 and SF-26 spectrophotometers (c = $10^{-4}$-$10^{-5}$ M). The PMR spectra were run on a Perkin-Elmer R-12 spectrometer (60 MHz) at 37°C, using HMDS as internal standard. The IR spectra of suspensions of the compounds in mineral oil were recorded on a UR-10 spectrophotometer.

2,4,6-Triamino-5-arylazopyrimidines (Ia, c, d-g, i-m). A solution of aryldiazonium chloride, obtained from 1 mmole of the corresponding amine, 11 mmoles of sodium nitrite, and 25 mmoles of conc. HCl, free of $HNO_2$, was added to a vigorously stirred solution of 12 mmoles

TABLE 4. 2,4,6-Triamino- and 2,4-Diamino-6-hydroxy-5-arylazo- and 5-Arylideneaminopyrimidines

| Compound | $R_f$ | Found N, % | Empirical formula | Calculated N, % | Yield, % |
|---|---|---|---|---|---|
| Ib | 0,78 | 34,8 | $C_{10}H_{10}N_8O_2$ | 34,9 | 50 |
| If | 0,66 | 38,9 | $C_{10}H_{10}ClN_7$ | 40,4 | 70 |
| Im | 0,59 | 39,2 | $C_{12}H_{16}N_8$ | 41,2 | 30 |
| IIk | 0,75 | 33,9 | $C_{11}H_{12}N_6O_2$ | 32,3 | 55 |
| IIm | 0,70 | 34,4 | $C_{12}H_{15}N_7O$ | 35,2 | 32 |
| IIIc | 0,63 | 34,8 | $C_{10}H_{11}N_7O_2$ | 36,2 | 65 |
| IIId | 0,55 | 31,5 | $C_{11}H_{12}N_6O$ | 32,0 | 75 |
| IVb | 0,80 | 29,3 | $C_{10}H_{10}N_6O_3$ | 30,7 | 40 |
| IVm | 0,58 | 29,6 | $C_{12}H_{16}N_6O$ | 30,9 | 56 |
| IVn | 0,60 | 27,7 | $C_{14}H_{20}N_6O$ | 28,0 | 48 |

of 2,4,6-triaminopyrimidine in 90 ml of water. The mixture was stirred for 1.5 h at ~20°C, while pH 6-7 was maintained by adding sodium acetate. The precipitate that separated was filtered, washed with ice water, and recrystallized from a 1:9 DMSO-$H_2O$ mixture. Yield 50-70%, mp > 300°C (Table 4).

2,4-Diamino-6-hydroxy-5-arylazopyrimidines (IIb, e, f, i-k, m) were obtained in a similar way and were purified by reprecipitation from an alkaline solution by a saturated solution of $NH_4Cl$. Yield, 50-70%, mp > 300°C (Table 4).

2,4,6-Triamino-6-benzylideneaminopyrimidines (IIIa-d, f, g-i, k, m, n). A 2 M hydrochloric acid was added at the boiling point to a solution of 10 mmoles of 2,4,5,6-tetraaminopyrimidine sulfate in 40 ml of 0.05 M hydrochloric acid to a complete dissolution of the material. A 10 ml portion of a 1 M solution of barium acetate was added gradually, in the course of 10 min, to the hot solution. The reaction for $Ba^{2+}$ ions was verified on the filter by rhodizonate. Excess $Ba^{2+}$ was removed by 0.1 M sulfuric acid. The barium sulfate precipitate that separated was filtered and a solution of 0.01 mole of benzaldehyde in 10 ml of alcohol was added at 50°C, with stirring, to the filtrate, the pH of which was adjusted to 4. After adding the aldehyde solution, a 0.1 M solution of NaOH was added to pH 8. The mixture was cooled, the precipitate was filtered, washed with ice water, alcohol, and ether. Yield, 50-60%.

2,4-Diamino-6-hydroxy-5-benzylideneaminopyrimidines (IVb, f, i, k, m, n). 2,4,5-Triamino-6-hydroxypyrimidine (10 mmoles) was dissolved in 40 ml of 0.05 M hydrochloric acid. The solution was heated to 50°C, and a solution of the corresponding aldehyde (10 mmoles) in 10 ml of alcohol was added to the hot solution. The pH of the solution was adjusted to 7.0, the mixture was cooled, and the azomethine was filtered, washed with cold water, alcohol and ether. Yield, 45-60%.

The individual state of the compounds obtained was confirmed by TLC. The ionization constants of compounds I were determined spectrometrically [19]. The concentration of the sulfuric acid solutions (2-77% by weight) was determined by potentiometric titration, using a pH-673 pH-meter. In measuring the $pK_{a1}$, a HCl glycine buffer mixture at pH 1.20-3.0 was used. The concentration of the compounds studied in the solutions was $10^{-4}$ M. Since the compounds studied are practically insoluble in water, the initial sample was first dissolved in 5 ml of DMSO, diluted with alcohol and then with water, so that the solution for the measurements would contain not more than 1% of DMSO and 5% of alcohol. The analytical wavelengths were selected from the results of the examination of the change in the UV spectra as a function of the acidity of the solution, so that the differences between the spectra of pure limiting forms were maximal. In general, a series of measurements was carried out on two analytical wavelengths.

The distribution coefficients of the compounds in the octanol—water system were determined spectrophotometrically [20]. Before the experiment, octanol (purified according to [20]) was saturated with water, and water with octanol. The solution of the compound studied in water saturated with octanol was introduced into the octanol—water system and the mixture was shaken for 10 min. The aqueous layer was separated from the octanol layer, centrifuged for 30 min (7000 rpm), and the optical density of the aqueous solution was measured on a SF-16 spectrophotometer on an analytical wavelength.

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# REDUCTION OF 12-ACETYLAMINOINDOLO[1,2-c]QUINAZOLINES. PREPARATION OF DERIVATIVES OF THE NEW HETEROCYCLIC SYSTEM INDOLO[3,2-d][1,3]BENZODIAZEPINE

S. Yu. Ryabova, A. N. Grinev,* and L. M. Alekseeva

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Reduction of derivatives of 12-acetylaminoindolo[1,2-c]quinazoline yielded the corresponding 12-acetylamino-5,6-dihydroindolo[1,2-c]quinazolines, recyclization of which under the influence of dilute hydrochloric acid led to the formation of derivatives of the hitherto unknown system indolo[3,2-d][1,3]benzodiazepine.

It is known that several of the aminoacyl derivatives of 12-aminoindolo[1,2-c]quinazoline possess sedative properties [1]. Extending the search for biologically active compounds into the indolo[1,2-c]quinazolines, we have studied the reduction of 12-acetylaminoindolo-[1,2-c]quinazolines Ia-d [2-4] by sodium borohydride in acetic acid. From the results of [5] one would expect that the amide group would here be reduced to a secondary amino group. However, we found that under these conditions 12-acetylamino-5,6-dihydroindolo[1,2-c]quinazolines (IIa-d) are formed in high yields. In other words, the C=N bond in the 1,2-position of the pyrimidine ring undergoes reduction. Reductive alkylation of the pyrimidine ring

*Deceased.

S. Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific Research Institute, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 668-673, May, 1988. Original article submitted October 23, 1986.

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