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Hydroxypyrimidines Condensation with Carbonyl Compounds: II.* Hydroxy-, Sulfanyl-, and Aminopyrimidines

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Abstract—The first part of review treated condensation of barbituric acids with carbonyl compounds both in the absence and in the presence of third components [1]. In so doing we discussed only the reactions involving the C^5 atom of the pyrimidine ring. The second part concerns similar transformations of other hydroxy- and aminopyrimidines and thioanalogs thereof.

I. URACILS

The uracil and its derivatives react with aldehydes to furnish depending on the structure of the latter and on the acidity of the medium two types of condensation products: either 5-hydroxymethyl derivatives or 5,5'-ylidenebisuracils. Apparently the former are precursors of the latter.

For instance, the uracil, uridine, and 2-deoxyuridine boiled in diluted hydrochloric acid with the highly reactive formaldehyde (paraformaldehyde) afford the corresponding 5-hydroxymethyl derivatives [2]. The 5-hydroxymethyluracil was also obtained when the reaction was carried out in diluted aqueous KOH [2].

In strongly acid medium (boiling concentrated hydrochloric acid) uracil undergoes condensation with aromatic aldehydes possessing strong electron-withdrawing substituents or with heterocyclic aldehydes providing 5-[(aryl or hetaryl)(hydroxy)methyl]- or 5-[(hetaryl)(hydroxy)methyl]-uracils (**1**) [3, 4].

The reaction of uracil under the same conditions with 6-methylpyridine-3-carbaldehyde or with benzaldehyde

gave rise to 5,5'-(R-methylene)bisuracils (**2**) [3]. However from the 6-methylpyridine-3-carbaldehyde this type compound formed alongside the hydroxymethyl derivative (**1**), but the only reaction product obtained from benzaldehyde was bispyrimidine (**2**) [3].

Compounds (**1**) may be reduced into the corresponding 5-(R^4-methyl)uracyls by catalytic hydrogenation in the presence of palladium on carbon, by boiling in formic acid, or by heating with sodium [4].

The introduction of a methyl group into position *6* of uracil favors formation of 5,5'-methylenebis(6-methyluracils) in the condensation with paraformaldehyde. For instance, the boiling of 6-methyluracils with paraformaldehyde in diluted hydrochloric acid resulted in the corresponding 5,5'-methylenebis derivatives (**2**) [5, 6]. Besides, compound (**2**, R^4 = Ph) was obtained in reaction of 6-methyluracil with benzaldehyde in the presence of a large excess of $ZnCl_2$ [7].

5,5'-Methylenebis(6-methyluracil) (**2**) also was obtained at room temperature from 6-methyluracil and formaldehyde in the presence of H_3PO_3 (acid medium) or

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* For communication I, see [1].
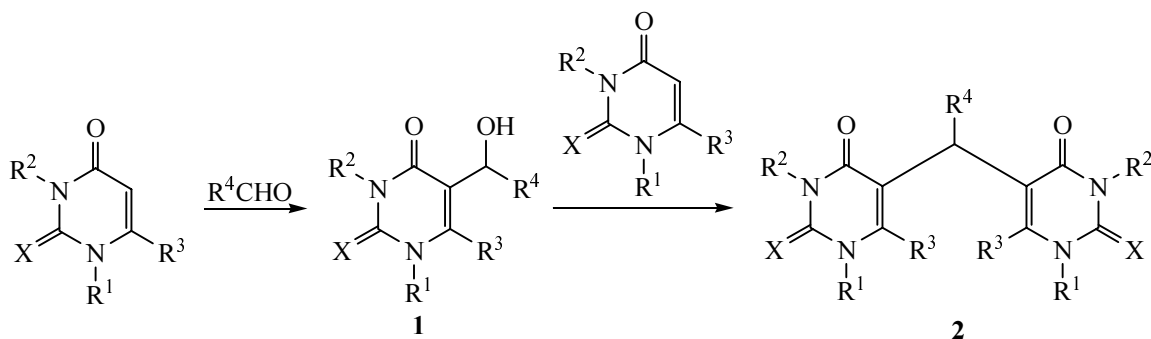
X = O, S, R^1 = H, CH$_2$ CH$_2$OH, β-*D*-ribofuranosyl, 2-deoxy-β-*D*-ribofuranosyl, Ph, R^2 = H, Me, Ph, R^3 = Me, Ph, R^4 = H, C$_6$H$_4$NO$_2$–4, pyridin-4-yl, 6-methylpyridin-3-yl, quinolin-3-yl, quinolin-4-yl

Na$_2$HPO$_3$ (alkaline medium) at prolonged storage (1.5–2 months). Alongside compound (**2**) in the alkaline medium formed 5,5'-methylenebis(6-methyluracil) whose molecule contained a CH$_2$OH group at an N^3 atom in one of the pyrimidine moieties [8].
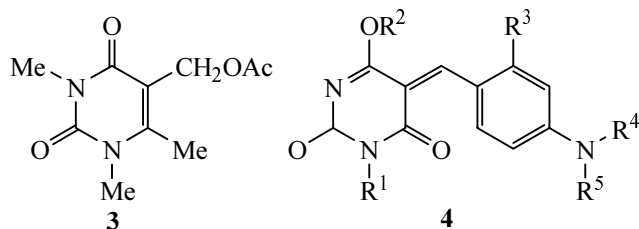
The reaction of 1,3,6-trimethyluracil with para-formaldehyde in the boiling acetic acid afforded as the main product the corresponding 5-acetoxymethyl-1,3,6-trimethyluracil (**3**) [5] alongside 5,5'-methyl-enebis(1,3,6-trimethyluracil) (**2**) and 5-hydroxymethyl-1,3,6-trimethyluracil (**1**) [5].

Thus at reduced electron-withdrawing effect of substituents or a heteroatom on the carbonyl group belonging to the carbonyl component a trend to the combination in a single product molecule of two pyrimidine moieties becomes stronger.

Reports on formation of 5-arylmethylene uracil derivatives common for barbituric acids appeared very seldom. Thus in reaction of 1-alkyl-6-alkoxyuracils with 4-dialkylaminobenzaldehydes in methanol in the presence of triethylamine 3-substituted 6-alkoxy-5-(arylmethylene)uracils (**4**) were obtained [9].

In the presence of lead(II) acetate 1,3-dimethyluracil reacted with acrolein diethyl acetal at the C=C bond of the latter affording 3-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acrylic aldehyde in 80% yield [10].

Reactions of uracil and its derivatives with bifunctional carbonyl compounds can result in formation of new rings. An intramolecular cyclization of 6-[2-(4,4-dimethyl-2,6-dioxocyclohexyl)ethyl]uracyl occurred in a mixture of HBr with acetic acid affording 9,9-dimethyl-6,8,9,10-tetrahydrobenzo[*f*][quinazoline-1,3,7-(2*H*,4*H*,5*H*)-trione (**5**) in 70% yield [11].

A similar cyclization fashion was observed in reaction of [[(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetra-hydropyrimidin-4-yl)methyl]lithium with α-oxoketones dithioacetals [12]. The corresponding 1,3-dimethyl-7-(methylthio)-quinazoline-2,4(1*H*,3*H*)-diones (**6**) were obtained in 73–86% yield.
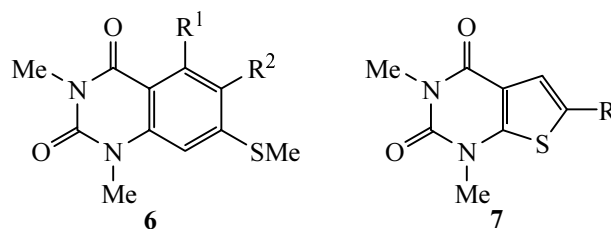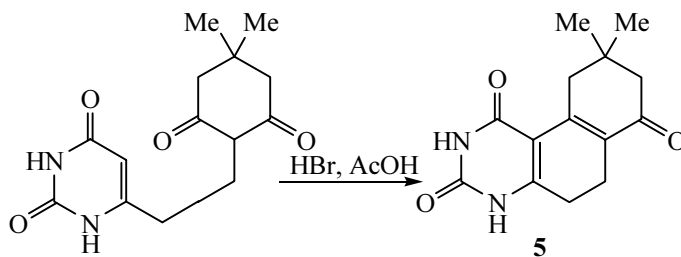

6, R^1 = Me, Ph, 2-furyl, R^1 = H, R^1, R^2 = (CH$_2$)$_4$; **7,** R = H, Br, NO$_2$, CHO

The heating of 6-methyluracil with aromatic aldehydes in acetic anhydride–acetic acid mixture gave rise to 5-aryl-4,6-dimethoxy-5.9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,8(1*H*)-diones (yield 40–82%) [13].
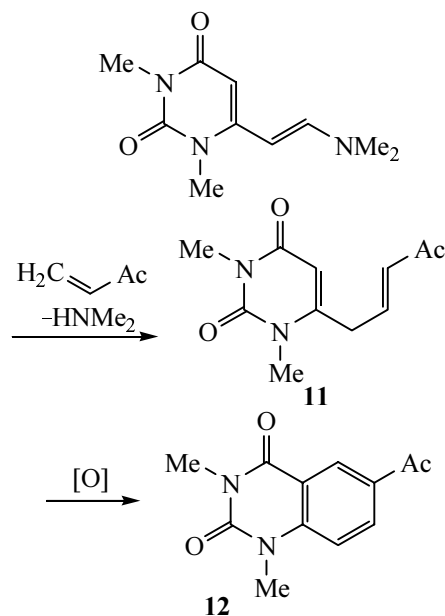
5,5'-Methylenebis(1,3-dimethyl-6-sulfanyluracil) in boiling ethanol in the presence of piperidine converts into 1,3,7,9-tetramethyl-5,9-dihydro-2*H*-thiopyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetrone in 61% yield [14].

The reaction of 1,3-dimethyl-6-sulfanyluracil with chloroacetaldehyde in water solution in the presence of sodium acetate afforded thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**7**, R = H) in 66% yield [15]. The latter was subjected to bromination, nitration, and formylation by Vilsmeier reaction to furnish respectively 6-bromo, 6-nitro, and 6-formyl derivatives (**7**).
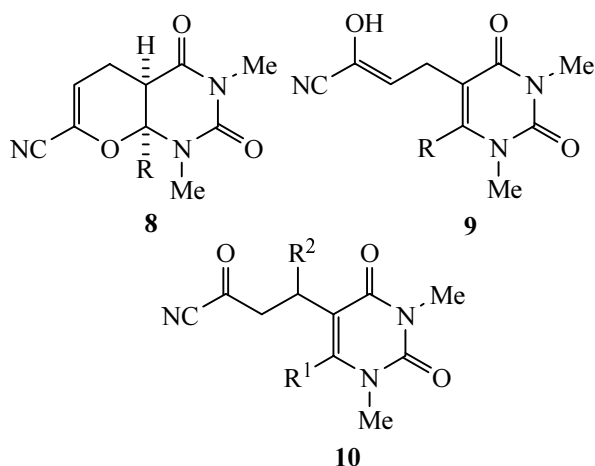
**8**, **9**, R = H, Me; **10**, R^1 = H, Me, R^2 = Me, CO$_2$Et.

The uracils enter in reactions with α,β-unsaturated carbonyl compounds. In this case the nucleophilic attack of C^5 uracil atom is directed on the β-position in the carb-

onyl compound. For instance, 1,3-dimethyl- and 1,3,6-tri-methyluracyls underwent hetero-Diels–Alder cyclo-addition with 2-oxo-3-butenonitrile to yield 2,4-dioxo-1,3,4,4*a*,5,8*a*-hexahydro-*cis*-2*H*-pyrano[2,3-*d*]pyr-imidine-7-carbonitriles (**8**) where the pyran ring readily opened in acid media [16]. Arising enols (**9**) are fairly stable and slowly isomerize into the respective ketones (**10**). It should be noted that the presence of substituents in the β-position with respect to carbonyl group of 2-oxo-3-butenonitriles (Me, CO$_2$Et) prevented formation of pyrano-pyrimidines of type (**8**). With these compounds the reaction finished at the stage of ketones (**10**) [16].

At heating in toluene of 6-[2-(dimethylamino)-vinyl]-1,3-dimethyluracil with 3-buten-2-one (methyl vinyl ketone) the carbonyl group of the latter was not involved in condensation. Here in 46% yield was obtained 6-acetyl-1,3-dimethylquinazoline-2,4(1*H*,3*H*)-dione (**12**) whose formation was accompanied by dimethylamine liberation and by oxidation of intermediate 5.8-dihydro derivative (**11**) [17].

From 3-methyl-6-chlorouracil and lithium 2-(di-meth-oxymethyl)selenophenolate a 2*H*-selenochrom-eno[2,3-*d*]-pyrimidine-2,4(3*H*)-dione was obtained in 7% yield [18].
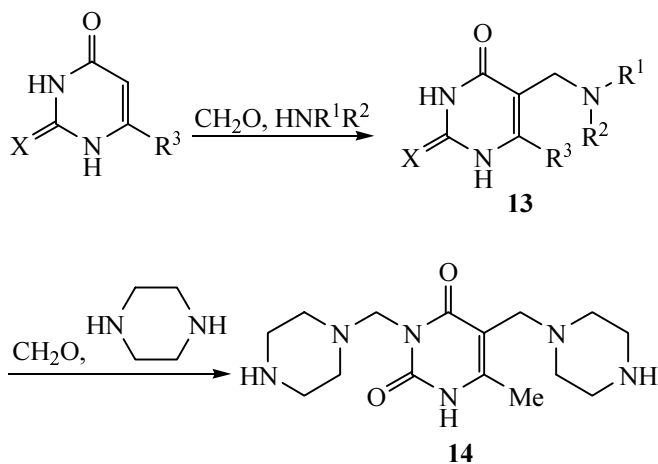

13, X = O, S; HNR^{1}R^2 dialkylamines, morpholine, piperidine, piperazine, 4-benzylpiperazine, 4-methyl-piperazine, 2-piperazin-1-ylethanol, R^3 = H, Me.

Uracil was brought into Mannich condensation with paraformaldehyde and secondary amines in boiling ethanol to afford the corresponding 5-(dialkylamino-methyl)uracils (**13**) in 65–85% yield [19].

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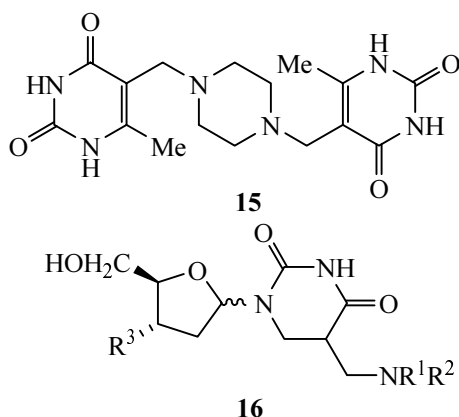
16, NR^{1}R^2 = dialkylamino, morpholino, piperidino, piperazin-1-yl, 4-benzylpiperazin-1-yl, 4-methyl-piperazin-1-yl.

6-Metyluracil and its 2-thioanalog in reaction with formaldehyde and morpholine, piperidine, and piperazine in ethanol or methanol furnished the corresponding Mannich bases (**13**) [20]. Mannich base (**13**) was also obtained from 5-hydroxymethyl-6-methyluracil and piperidine [20]. At excess formaldehyde and piperazine the N^3 atom of 6-methyluracil is also involved into the process [20] affording compounds (**14**).


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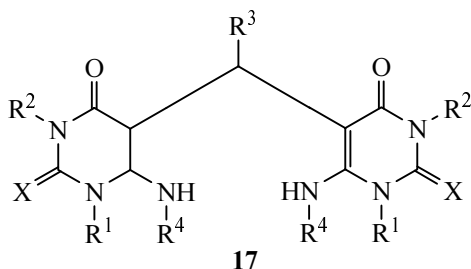
X = O, S, R^1 = H, Me, R^2 = H, Me, CH$_2$C(O)NHMe, R^3 = H, Me, Et, MeCH=CH, CO$_2$Et, (CHOH)$_3$CH$_2$OH, PhCH=CH, Ph, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-HOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3,4-(CH$_2$O$_2$)$_2$C$_6$H$_3$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 4-FC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, C$_6$F$_5$, 4-NCC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-(4-ClC$_6$H$_4$)C$_6$H$_4$, 4-(4-O$_2$NC$_6$H$_4$)C$_6$H$_4$, 2-naphthyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, R^4 = H, Me, Pr, Bu, CH$_2$Ph. R = H, Me, R' = H, (CHOH)$_3$CH$_2$OH, Ph, 4-ClC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-HOC$_6$H$_4$, 2-MeOC$_6$H$_4$, 2-furyl, CO$_2$Et.

At a molar ratio piperazine–formaldehyde–6-methyluracil = 1:2:2 both piperazine nitrogens are involved into the reaction to provide compound (**15**) [20].

Some of Mannich bases (**13**, X = O) were converted in azidothymidine analogs (**16**) [19].

II. 6-AMINOPYRIMIDIN-4(3*H*)-ONES

Reports on azomethines formation from 6-amino-uracils (at amino group) and carbonyl compounds are scarce, for instance, concerning 3-formylchromone [21] or 5-(2-carboxyphenylsulfonyl)thiophen-2-carbaldehyde [22].

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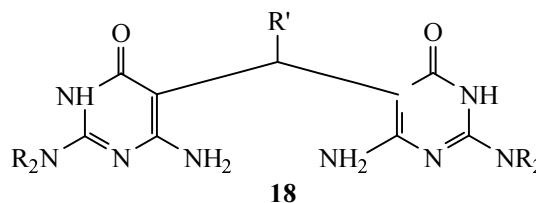
R = H, Me, R' = H, (CHOH)$_3$CH$_2$OH, Ph, 4-ClC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-HOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 2-furyl, CO$_2$Et.

In water, ethanol, and acetic acid the 6-aminouracils with aliphatic and aromatic aldehydes, ethyl (hydroxy)ethoxyacetate and also with *D*-arabinose give 5,5'-ylidenebis(6-aminouracils) (**17**) in 16–95% yield [23–33]. In a similar fashion 6-amino-2-thiouracil underwent condensation with formaldehyde and benzaldehyde [25].

2,6-Diaminopyrimidin-4(3*H*)-ones with aliphatic, aromatic, and heterocyclic aldehydes or their acetals [25], and with *D*-arabinose [33] at heating in water also afford the corresponding 5,5'-ylidenebispyrimidines (**18**).

6-Amino-2-(methylthio)pyrimidin-4(3*H*)-one and its 1,3-dimethyl derivative with formaldehyde and benzaldehyde in water or methanol give 5,5'-methylene-(benzylidene)bis[6-amino-2-methyl-sulfanylpyrimidine-4(3*H*)-ones] similar to compounds (**17**) [14, 25].

The presence of dialkylamino groups in the position *6* of uracil totally prevent the condensation to forn bisuracils (**17**) apparently due to arising steric hindrances.

In some cases it was possible to obtain from 6-amino-pyrimidine-4(3*H*)-ones and aromatic aldehydes the corresponding 5-arylmethylene derivatives. For instance, 2,6-diaminopyrimidin-4(3*H*)-one and 3,5-dimethoxy-4-(2-methoxyethoxy)benzaldehyde furnished 2,6-diamino-5-{[3,5-dimethoxy-4-(2-methoxyethoxy)phenyl]-methylene}pyrimidin-4(5*H*)-one [34].

6-Amino-2-(methylthio)pyrimidin-4(3*H*)-one at boiling in concentrated hydrochloric acid with 6-methyl-pyridine-3-carbaldehyde afforded 5-[hydroxy(6-methyl-3-

pyridyl)methyl]-2-(methylthio)pyrimidin-4(3*H*)-one [4]. At heating the latter with a metallic zinc in acetic acid occurred both reduction of CHOH group into CH$_2$ and hydrolysis of MeS moiety resulting in 5-(6-methyl-3-pyridyl)-methyluracil [4].

In contrast to the above carbonyl compounds, *D*-glucose and *D*-mannose with 6-aminouracil and 2,6-di-aminopyrimidin-4(3*H*)-one at prolonged heating in boiling water gave the corresponding 5-(*D*-glycopyranoz-yl) derivatives of these pyrimidines in 31–55% yields. It should be noted here, that reaction with the 6-aminouracil furnished 6-amino-5-(α-*D*-glucopyranozyl)uracil whereas from 2,6-diaminopyr-imidin-4(3*H*)-ones only β-anomers were obtained [33].


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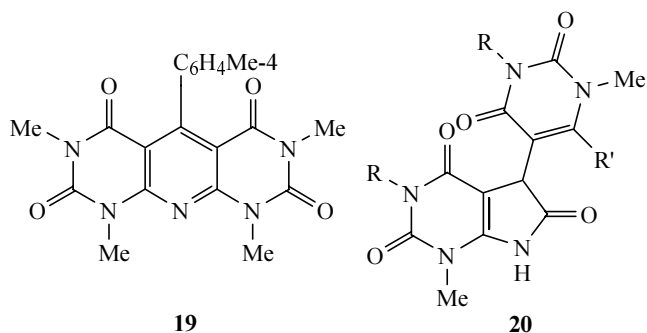
20, R = H, Me, R' = NH$_2$, OH.

Compounds (**17**) containing primary amino groups in the pyrimidine rings on heating in the absence of oxidants suffer cyclization into pyrido[2,3-*d*:6,5-*d'*]-dipyrimidine derivatives. For instance, 5,5'-(*p*-tolyl-methylene)-bis(6-amino-1,3-dimethyluracil) heated in sulfolane at 200°C converted into 1,3,7,9-tetramethyl-5-(*p*-tolyl)pyrido[2,3-*d*:6,5-*d'*]-dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone (**19**) [31]. Similar compounds were also obtained as side products of 5,5'-meth-ylenebis(6-aminouracils) hydrolysis [25].

Ethyl bis(6-amino-2,4-dioxo-1,2,3,4-tetrahydropyr-imidin-5-yl)acetates (**17**, R^3 = CO$_2$Et) prepared by 6-aminouracils condensation with ethyl (hydroxy)(ethoxy)-acetate are converted by heating in alkaline medium into 5,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4,6(3*H*)-trione derivatives (**20**) [30]. A similar compound (**20**, R = Me, R' = OH) was obtained at heating in water 6-amino-1,3-dimethyluracil with the chloral hydrate [30].

At treating 5,5'-(aryl)methylenebis(6-aminouracils) (**17**) with oxidants, e.g., diethyl diazenedicarboxylate,

21   **22**
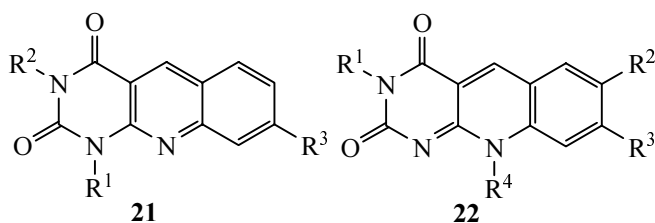
21, R^1 = Me, R^2 = Me, R^3 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$; **22**, R^1 = Me, CH$_2$C(O)NHMe, R^2 = H, Me, MeO, Cl, R^3 = H, Me, OH, MeO, Cl, NO$_2$, CN, Ph, 4-O$_2$NC$_6$H$_4$, R^2,R^3 = CH$_2$O$_2$, R^4 = H, Me, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 3,4-Me$_2$C$_6$H$_3$.

in sulfolane at 160–180°C occurred elimination of one of pyrimifine fragment, and a pyridine ring closed at the cost of one *ortho*-position in the benzene ring. In the presence in position *6* of pyrimidine ring of a primary amino group form pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones (5-deazaalloxazines) (**21**) [31]. In case the amino group is secondary the oxidation products are pyrimido[4,5-*b*]-quinoline-2,4(3*H*,10*H*)-diones (5-de-azaflavins) (**22**) (yield 45–80%) [23, 24, 27, 28]. Note that at the absence of substituents in position *3* of pyrimidine fragments in compounds (**17**, R^2 = H) the oxidative cyclization is considereably complicated by degradation of the inithial compounds [23].

The same transformations pattern exists in the analogous oxidation of bispyrimidines (**17**) prepared from 2-naphthoic aldehyde, thiophencarboxaldehyde, and nicotinaldehyde and 3-methyl-6-(methyl-amino)uracil. As a result 3,12-dimethylbenzo[*h*]quino-lino[2,3-*d*]pyrimidine-2,4(3*H*,12*H*)-dione, 3,9-di-methylthieno[2',3':5,6]pyrido[2,3-*d*]pyrimidine-2,4-(3*H*,9*H*)-dione, and 3,10-dimethylpyrimido[4,5-*b*]-1,8-naphthiridine-2,4(3*H*,10*H*)-dione were respectively obtained in 74–83% yield [27]. However the oxidation of bispyrimidines (**17**) prepared from picolinaldehyde and isonicotinaldehyde and 3-methyl-6-(methylamino)-uracil gave 3,7,10-trimethylpyrido[2,3-*d*:6,5-*d'*]dipyr-imidine-2,4,6,8(1*H*,3*H*,7*H*,10*H*)-tetrones (**42**, R^1 = 2-pyridyl, 4-pyridyl) [27].

The oxidation at higher temperature (200°C) with diethyl diazenedicarboxylate of 5,5'-(aryl)-methylenebispyrimidines (**17**) obtained from 6-anilino-uracils the 5-aryl-3-methylpyrimido[4,5-*b*]quinoline-2,4-(3*H*,10*H*)-diones formed as minor products. These compounds are the main products arising at heating the corresponding bispyrimidines (**17**) in sulfolane at 250°C without oxidants (yield 89–92%) [28]. Obviously

here the pyridine ring is built up from the aryl of the aniline moiety and not from that in the aldehyde.

The reaction of 6-glycosylaminopyrimidines and chloroacetaldehyde in boiling water in the presence of sodium acetate gave rise to 7-glycosylpyrrolo-[2,3-*d*]-pyrimidines (**23**) in 32–62% yield [35]. However this reaction with 2-methoxy-6-(tetraacetyl-β-*D*-gluco-pyranosylamino)pyrimidin-4-(3*H*)-one did not proceed regiospecifically, and alongside compound of (**23**) type a furopyrimidine derivative (**24**) was obtained in 39% yield [35]. It is assumed that in this conversion first alkylation of pyrimidine ring at the C^5 atom takes place followed by a cyclization of the intermediate product at the cost either of the amino group nitrogen or of the carbonyl oxygen.

23   **24**
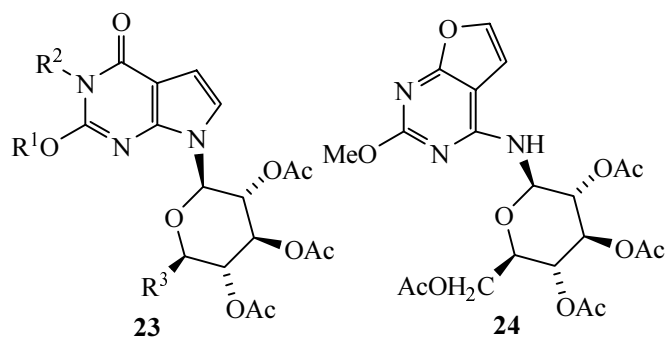
R^1 = H, Me; R^2 = H, Me; R^3 = H, CH$_2$OAc.

25   **26**

27   **28**
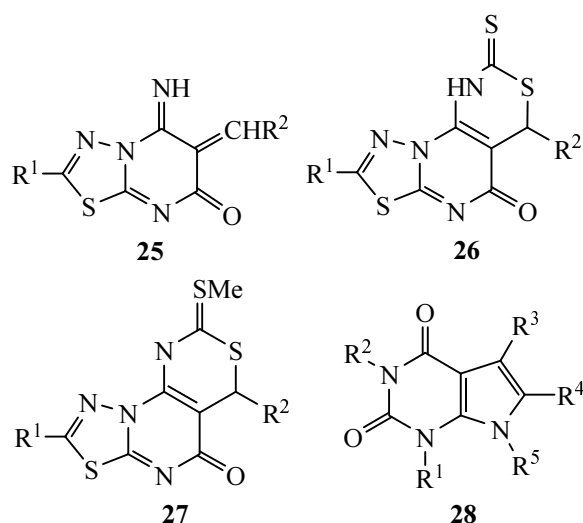
25–27, R^1 = H, Me, R^2 = Ph, 4-FC$_6$H$_4$, 2-furyl; **28**, R^1 = H, Me, Et, Pr, CH$_2$CH=CH$_2$, Bu, CH$_2$Ph, Ph, 4-MeC$_6$H$_4$, R^2 = H, Me, Pr, R^3 = H, Me, Et, *i*-Pr, Bu, *i*-Bu, C$_5$H$_{11}$, Ph, CH$_2$CO$_2$Me, R^4 = H, Me, Et, Pr, Ph, R^3, R^4 = (CH$_2$)$_3$, R^5 = H, Me.

29   **30**
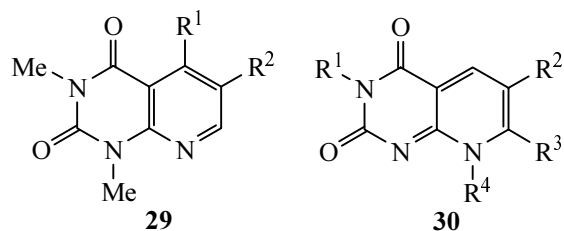
29, R^1 = Me, Et, Ph, 4-ClC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, R^2 = H, Me, Et, R^1, R^2 = (CH$_2$)$_{3-6}$; **30**, R^1 = Me, R^2 = Me, CO$_2$Et, R^3 = Me, Et, Ph, R^2, R^3 = (CH$_2$)$_4$, R^4 = Me, Bu, C$_8$H$_{17}$, Ph.

The reaction between 2-R-5-imino-5,6-dihydro-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-7-ones and aromatic or heterocyclic aldehydes in the presence of triethylamine furnishes 6-(R-methylene)-5-imino-7*H*-[1,3,4]thiadi-azolo[3,2-*a*]-pyrimidin-7-ones (**25**). Further by treating with CS$_2$ or with CS$_2$ and methyl iodide these compounds were converted into 2,6-disubstituted 5*H*,6*H*-[1,3,4]thiadiazolo[2',3':2,3]pyrimido[4,5-*d*]-[1,3]thiazin-5-ones (**26**, **27**) respectively [36].
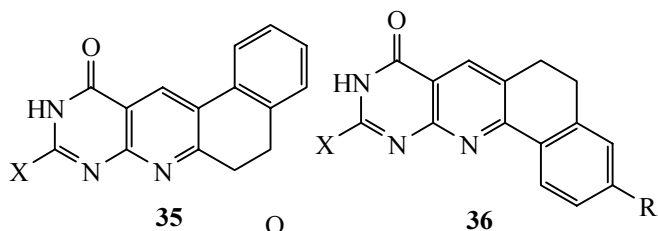
The condensation of 6-aminouracils together with aliphatic or aromatic aldehydes and dimedone afforded 5-alkyl(aryl)-8,8-dimethyl-2,4,6-trioxo-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-*b*]quinolines that were also prepared from 5-(arylmethylene)barbituric acids and 3-amino-5,5-dimethyl-2-cyclohexenone [37, 38].

31   **32**

33   **34**
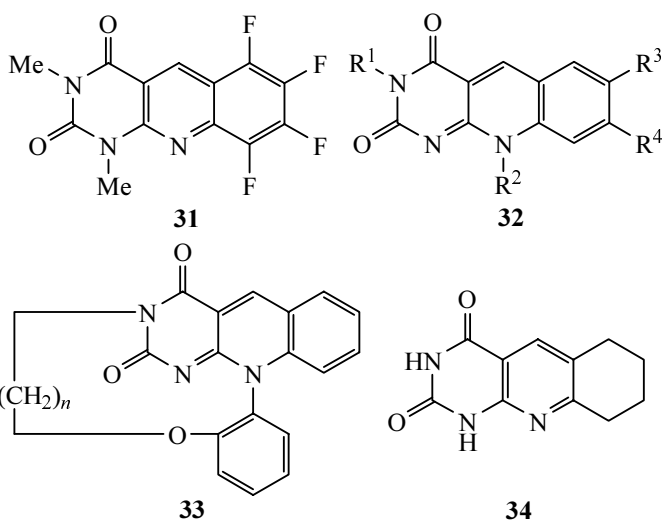
32, R^1 = H, Me, Ph, 2-MeC$_6$H$_4$, 2-EtC$_6$H$_4$, 2-*i*-PrC$_6$H$_4$, 2-*t*-BuC$_6$H$_4$, 2-F$_3$CC$_6$H$_4$, 2,4,6-Br$_3$C$_6$H$_2$, 2,4-Br$_2$-6-MeC$_6$H$_2$, 1-naphthyl, R^2 = Me, Pr, Bu, C$_8$H$_{17}$, C$_{12}$H$_{25}$, C$_6$H$_{11}$, CH$_2$Ph, Ph, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-*t*-BuC$_6$H$_4$, 2,4-Me$_2$C$_6$H$_3$, 3,4-Me$_2$C$_6$H$_3$, 4-ClC$_6$H$_4$, 2-HOC$_6$H$_4$, R^3 = H, NO$_2$, R^4 = H, Cl, OH; **33**, *n* = 6, 8, 10, 12.
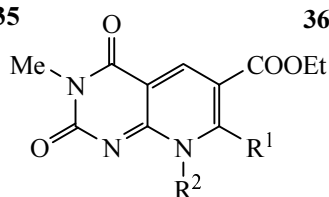
1,3-Disubstituted 6-aminouracils with α-halogenated carbonyl compounds (chloroacetaldehyde etc.) afford 1*H*-pyrrolo-[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione deriv-atives (**28**) in 11–82% yield [39]. The pyrrole ring results here from alkylation of the amino group in aminouracil and from coordination to the C^5 atom in pyrimidine of the carbonyl group from the carbonyl component. The pyrrole nitrogen in compounds (**28**) undergoes methylation with dimethyl sulfate, and hydrogenation of these compounds on Pd-C furnishes 5,6-dihydro-derivatives.

The condensation of 6-aminouracils with aromatic aldehydes possessing a halogen in the *ortho*-position, or with α,β-unsaturated β-halocarbonyl compounds not only involves the C^5 atom of pyrimidine and the carbonyl group of the aldehyde or ketone, but as a rule is followed by a further cyclization affording a pyridine ring due to nucleophilic replacement of the halogen by amino group (or due to addition–elimination). As a result of these processes form pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones. For instance, the heating in DMF of 6-amino-uracils with α,β-substituted β-chloroacrylic aldehydes gave rise to pyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione derivatives (**29**) [40] or to pyrido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-dione derivatives (**30**) in 52–91% yield [41].
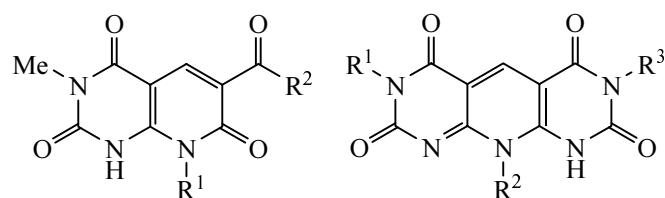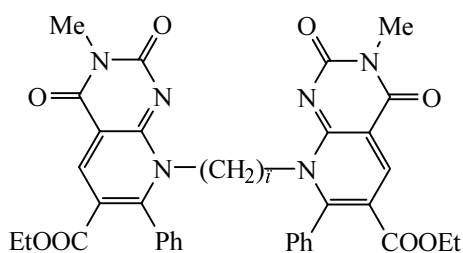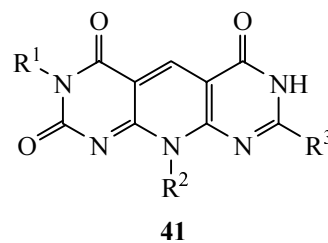
6-Alkyl(aryl, aralkyl)aminouracils and *o*-fluoro-(chloro, bromo)benzaldehydes heated in DMF afforded pyrimido[4,5-*b*]quinoline-2,4-(3*H*,10*H*)-diones (5-deaza-flavins) (**32**) in 41–99% yield [42–49]. This reaction was successfully carried out with 6,6'-[alkane-1,*n*-diyldi-(imino)]diuracils to obtain the corresponding 10,10'-(alkane-1,*n*-diyl)-di{pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones} (*n* = 6, 8, 10, 12) in 34–70% yield [43]. The heating of 6-amino-1,3-dimethyluracil with pentafluorobenzaldehyde in the acetic acid resulted in 1,3-dimethyl-6,7,8,9-tetrafluoropyrimido[4,5-*b*]-quinoline-2,4(1*H*,3*H*)-dione (**31**) [29, 50]. It should be noted however that the presence of electron-withdrawing fluorine atoms in other positions of the benzene ring is essential for the *o*-fluorobenzaldehyde does not yield under these conditions the corresponding tricyclic product. The *o*-fluorobenzaldehyde was involved into the reaction by heating the reagents in DMF [47].

The reaction presumably proceeds through an intermediate formation of 5,5'-arylmethylenebis derivative that at heating eliminates one pyrimidine fragment giving 6-amino-5-arylmethyleneuracils. Just the latter undergo cyclization into 5-deazaflavins [43].

The alkylation of 10-(2-hydroxyphenyl)pyrimido-[4,5-*b*]quinoline-2,4(3*H*,10*H*)-dione (**32**, R^1 = R^3 = R^4 = H, R^2 = 2-HOC$_6$H$_4$) with 1,8-dibromooctane or with 1,10-dibromodecane provided in 4–27% yield optically active 5-deazaflavinophanes (**33**) [44, 48, 49].

35

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35, **36**, X = OH, NH$_2$, R = MeO; **37**, R^1 = Me, Ph, R^2 = Me, Bu, C$_8$H$_{17}$, Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$; **38**, *n* = 6, 8, 10, 12.

R^1 = H, Me, Et, Bu, C$_{16}$H$_{33}$, CH$_2$Ph, Ph, R^2 = Me, Et, Pr, Bu, C$_8$H$_{17}$, C$_{12}$H$_{25}$, C$_{18}$H$_{37}$, CH$_2$CH$_2$Ph, Ph, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 2,6-Me$_2$C$_6$H$_3$, 3,4-Me$_2$C$_6$H$_3$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-MeOC$_6$H$_4$, R^3 = H, Me, Et, Ph.

The 6-aminouracil reacts with 2-chloro-1-cyclo-hexenecarbaldehyde regioselectively affording tricyclic 6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline-2,4-(1*H*,3*H*)-dione (**34**) of a linear structure [51]. 6-Amino-uracil or 2,6-diaminopyrimidin-4(3*H*)-one and 2-chloro-3,4-dihydronaphthalene-1-carbaldehyde heated in acetic acid furnished the corresponding benzo[*f*]pyrimido[4,5-*b*]quinolines (**35**) in 55–94% yield [52], and in a similar reaction with 1-chloro-3,4-dihydronaphthalene-2-carb-aldehyde formed 5,6-dihydro-benzo[*h*]pyrimido[4,5-*b*]quinolines(**36**) in 65–83% yield [53]. Heating in DMF 6-R-amino-1-methyluracil with ethyl (2*E*)-2-formyl-3-chloro-2-butenoate or ethyl (2*E*)-3-phenyl-2-formyl-3-chloroacrylate gave ethyl 3-methyl-2,4-dioxo-2,3,4,8-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylates (**37**, **38**) in respective yield 75–91 and 89–92% [54].

The reaction between 6-amino-1,3-dimethyluracil and ethyl (2*E*)-3-phenyl-2-formyl-3-chloroacrylate gave rise to ethyl 1,3-dimethyl-2,4-dioxo-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylate [54].

Compounds (**37**, **38**) under treatment with ethanol solution of KOH or with primary amines suffer a rearrangement into 6-acylpyrido[2,3-*d*]pyrimidine-2,4,7-(1*H*,3*H*,8*H*)-triones (**39**) (yield 79–90%) or into their imines [54].

42   **43**
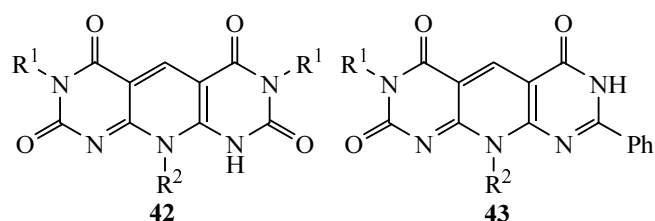
R¹ = H, Me, Ph, R² = Me, Et, Pr, Bu, C_8H_{17}, $C_{12}H_{25}$, $C_{18}H_{37}$, CH_2CH_2Ph, Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 3,4-Me$_2$C$_6$H$_4$.

Heating 6-R-aminouracils or 6-R-aminopyrimidin-4(3*H*)-ones with 3-R-2,4-dioxo-6-halo-1,2,3,4-tetra-hydropyrimidine-5-carbaldehydes in acetic acid, ethyl acetate, or DMF provided respectively pyrido[2,3-*d*:6,5-*d*']-dipyrimidine-2,4,6,8(3*H*,7*H*,9*H*,10*H*)-tetrones (**40**) and pyrido[2,3-*d*:6,5-*d*]dipyrimidine-2,4,6(3*H*,7*H*, 10*H*)-triones (**41**) [55–59]. Similar compounds formed also from 6-R-aminouracils or 6-R-aminopyrimidin-4(3*H*)-ones in reaction with 2,4,6-trichloropyrimidine-5-carbaldehyde carried out in acetic acid [58, 60]. The reaction occurred cleanly also between 2,4-dioxo-6-halo-1,2,3,4-tetrahydropyrimidine-5-carbaldehydes or 2,4,6-trichloropyrimidine-5-carbaldehydes and 6,6'-[alkane-

1,*n*-diyldi(imino)]diuracils or   -di[pyrimidin-4(3*H*)-ones] [61,62]. The corresponding 10,10'-(alkane-1,*n*-diyl)di{pyrido[2,3-*d*:6,5-*d*']dipyrimidines} (*n* = 6, 8–10, 12) were obtained in 19–63% yield.

44   **45**
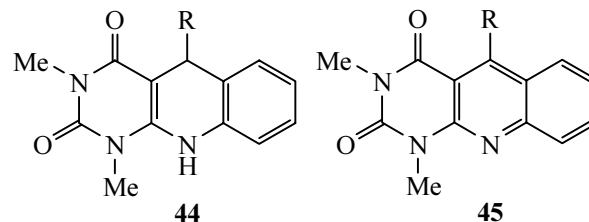
R = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$.

In the reaction of 6-aminouracils with 5-formyl-6-chlorouracils [57, 61, 63] or 3-methyl-6-chlorouracil with 6-(R-amino)-3-methyl-5-formyluracil [64] in DMT at 200–220°C a heterocyclic system is built up where the pyridine ring is fused to two pyrimidine ones to give 10-R-pyrido[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8-(1*H*,3*H*,7*H*,10*H*)-tetrones (**42**) in 61–85% yield. Compounds of this series were prepared in 65–78% yield by reaction of 6-amino-uracils with 2,4,6-trichloro-pyrimidine-5-carbaldehyde [63].

The reaction between 6-amino-2-phenylpyrimidin-4(3*H*)-ones with 5-formyl-6-chloro-uracils or 2,4,6-tri-chloropyrimidine-5-carbaldehyde in acetic acid proceeds in a similar fashion [63]. The products thereof are 10-R-8-phenylpyrido[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6-(3*H*,7*H*,10*H*)-triones (**43**) (yield 45–94 %).


46   **47**
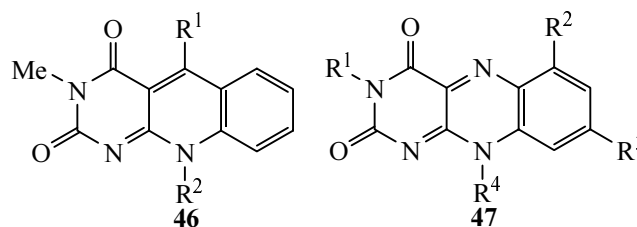
46, R¹ = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-O$_2$NC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, R² = Me, Et; **47**, R¹ = H, Me, R² = H, Me, R³ = H, Cl, OMe, R⁴ = Me, Et, Ph, 3-MeC$_6$H$_4$, 3,4-Me$_2$C$_6$H$_3$, 4-ClC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 2-HOC$_6$H$_4$, 4-HOC$_6$H$_4$, 2-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-AcOC$_6$H$_4$, 4-NCC$_6$H$_4$, PhCH$_2$, PhCH$_2$CH$_2$, AcOCH$_2$CH$_2$, AcO(CH$_2$)$_3$, Pr, Bu.

Compounds (**42**, **43**) are readily reduced with sodium dithionite or with alcohols into the corresponding 1,5-dihydro derivatives [63].

6-(Arylamino)uracils can be condensed with aromatic aldehydes building up a pyridine ring from one of the *ortho*-positons of the arylamino group and the C^5 atom

of the pyrimidine ring. For instance, heating a mixture of 6-anilino-1,3-dimethyluracil with aromatic aldehydes gives rise to 5-aryl-1,3-dimethyl-5,10-dihydropyrimido-[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones (**44**) that at heating with thionyl chloride or diethyl diazenedicarboxylate are oxidized into 5-aryl-1,3-dimethylpyrimido[4,5-*b*]-quinoline-2,4(1*H*,3*H*)-diones (**45**) [65].
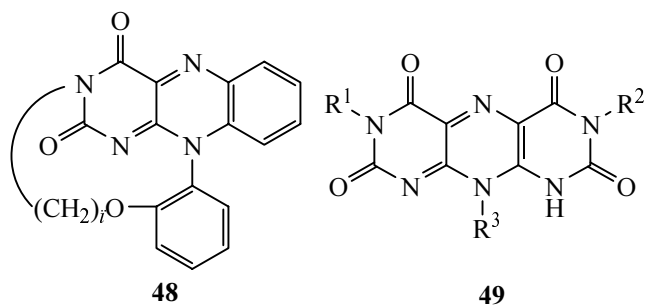
48, *n* = 6–8, 10, 12; **49**, R^1 = H, Me, R^2 = H, Me, R^3 = Me, Pr, Bu, C_8H_{17}, $C_{12}H_{25}$, Ph, 2,4-Me$_2$C$_6$H$_3$, 4-ClC$_6$H$_4$, 3-HOOCC$_6$H$_4$

With no substituent in position *1* the 6-(aryl-amino)uracil containing a tertiary amino group reacts in the polyphosphoric acid along the same pathway of condensation and cyclization; however the oxidation stage that does not require special oxidants (the oxidation is effected by the air oxygen) yields as products 5-de-azaflavins (**46**) [66].

Heating in a mixture of acetic acid and acetic anhydride of 6-R-aminouracils containing no substituent in position *1* with nitrosobenzenes, these azaanalogs of aromatic aldehydes, furnishes 10-R-isoalloxazines (**47**) in 25–75% yield [48, 67–74]. The ring closure occurs at the *ortho*-position of the nitrobenzene and involves dehydrogenation of intermediates effected by excess nitroso compound.

At alkylation of 10-(2-hydroxyphenyl)isoalloxazine (**47** R^1 = R^2 = R^3 = H, R^4 = 2-HOC$_6$H$_4$) with 1,*n*-di-bromoalkanes in DMF at 80–90°C flavinophanes (**48**) were obtained in 2–10% yield [48].

Violuric acids with 6-aminouracils [75] and 6-amino-5-nitrosouracils with 6-chlorouracils [76] at heating in DMF provide pyrimido[5,4-*g*]pteridine-2,4,6,8-(1*H*,3*H*,7*H*,10*H*)-tetrones (**49**) in 56–72% yield.

In reaction of 1,3-dimethyl-5-nitro-6-chlorouracil with 6-amino-1,3-dimethyluracil, 6-amino-3-methyl-2-phen-yl(or methylthio)pyrimidin-4(1*H*)-one in boiling DMF formed respectively derivatives of pyrimido[5,4-*g*]-pteridine-2,4,6,8-(1*H*,3*H*,7*H*,9*H*)-tetron-5-oxide or
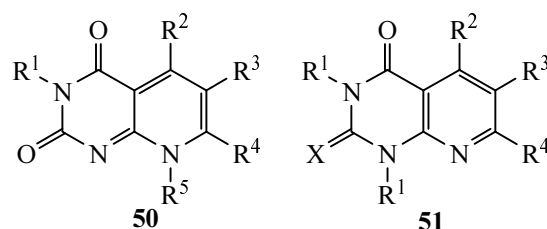
50, R^1 = H, Me, R^2 = H, Me, Ph, R^3 = H, Me, R^4 = H, Me, Ph, R^5 = CH$_2$CH$_2$OH, Ph, D-ribityl; **51**, X = O, S, R1 = H, Me, R^2 = H, Me, Ph, R^3 = H, Me, Pr, Bu, C_5H_{11}, R^4 = H, Me, t-Bu, Ph.

8-phenyl(or methylthio)pyrimido[5,4-*g*]pteridine-2,4,6(1*H*,3*H*,7*H*)trion-5-oxides that under treatment with NaHSO$_3$ were reduced into derivatives of pyr-imido[5,4-*g*]pteridine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone or 8-phenyl(or methylthio)pyrimido[5,4-*g*]pteridine-2,4,6(1*H*,3*H*,7*H*)-trione [77].
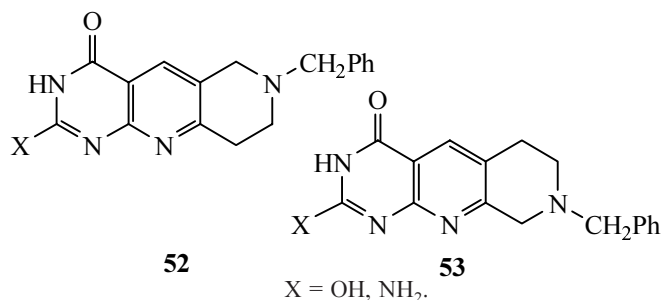

X = OH, NH$_2$.

With the β-dicarbonyl compounds [78, 79] the 6-aminouracils possessing secondary or primary amino groups furnish respectively pyrido[2, 3-*d*]pyrimidine derivatives (**50**, **51**). For instance, 6-anilinouracils with 2,4-pentanedione, 1-phenylbutane-1,3-dione or and 1,3-diphenylpropane-1,3-dione give 8-phenylpyrido[2,3-*d*]-pyrimidine-2,4(3*H*,8*H*)-diones (**50**) in 51–83% yield [78, 79]. The reaction with 6-benzylamino-3-methyluracil is accompanied with the substrate debenzylation to afford 3-methylpyrido-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**51**), phervenulin analog [78]. 6-Methylamino-, 6-ethyl-amino-, 6-propylamino-, and 6-butylamino-3-methyl-uracils did not react with 2,4-pentanedione or malonaldehyde tetramethylacetal [78]. In reactions with β-oxoaldehydes (or their acetals) the aldehyde group of the latter coordinates to the C^5 atom, and the keto group coordinates to the amino group of the 6-aminouracils, their 2-thio and 2-imino analogs [80–83].

The cyclocondensation of 6-aminouracil or 2,6-di-aminopyrimidin-4(3*H*)-one with the sodium salt of

1-benzyl-3-hydroxymethylene-4-piperidone follows the same pattern (amino group in the aminopyrimidine coordinates regiospecifically to the carbonyl group of the piperidone). As a result formed derivatives of 6,7,8,9-tetrahydropyrimido[4,5-*b*][1,6]naphthiridine (**52**) [84]. The derivatives of 6,7,8,9-tetrahydropyrimido-[4,5-*b*]-[1,7] naphthiridine (**53**) were prepared by this procedure from the 1-benzyl-4-hydroxymethylene-3-piperidone sodium salt [85].

As another example of this process may serve the formation of 5,6-dihydrobenzo[*h*]pyrimido-[4,5-*b*]-quinolines (**36**) in reaction of 6-aminouracil and 2,6-di-aminopyrimidin-4(3*H*)-one with the sodium salt of 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carbaldehyde in 85% phosphoric acid in 85–95% yield [53].
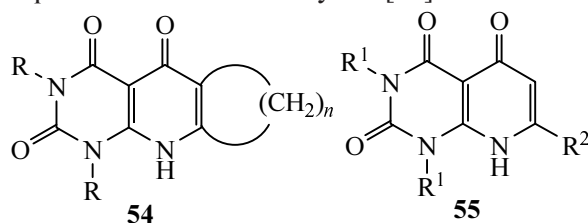

**54,** *n* = 3, 4, R = Me, Ph; **55,** R^1 = Me, Ph, R^2 = Me, Ph.

In reaction of 6-aminouracils with β-oxocarboxylic acids esters the building up of a pyridine ring fused to pyrimidine one occurs by an attack of the amino group of aminouracil on the carbonyl function of the ester and acylation of the C^5 atom of the pyrimidine. Thus, 1,3-disubstituted 6-aminoouracils in reactions with ethyl acetoacetate, benzoylacetate 2-oxocyclopentanecarb-oxulate, and 2-oxocyclohexanecarboxylate in boiling phenyl ether were converted into pyrido[2,3-*d*]-pyrimidine-2,4,5(1*H*,3*H*,8*H*)-triones (**54**, **55**) in 64–92% yield [86].

In the course of reactions with α,β-unsaturated aldehydes or ketones (chalcones, 1-phenyl-2-butene-1-one etc.) the amino group of the 6-aminouracils attacks the carbonyl group of the carbonyl compound, and the C^5 atom adds to the β-position of the latter building up the pyrido[2,3-*d*]pyrimidine system, as occurs also with β-dicarbonyl compounds. When the process is carried out in 20% hydrochloric acid, in alcohols, or without solvent, in the presence of bases (sodium ethylate, piperidine) the 6-aminouracils with a primary amino group afford pyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-diones (**51**), and those with a secondary amino group give pyrido[2,3-*d*]pyrimidine-2,4(3*H*,-8*H*)-diones (**50**) [32, 80, 87, 88]. Therewith apparently a necessary stage is oxidation (autooxidation) owing to which a non-

aromatic six-membered nitrogen-containing ring becomes aromatic.
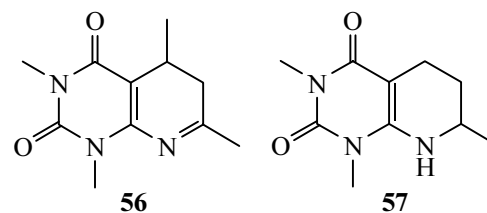
Wawzonek [32] suggested that in these processes the part of intermediates played 5,6-dihydro derivatives (**56**) that in their turn underwent disproportionation affording pyridopyrimidines (**51**) and 5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**57**).
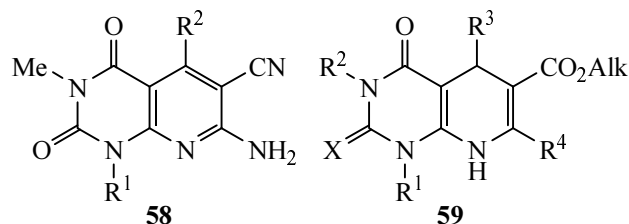
58, R^1 = H, Me, R^2 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$; **59**, X = O, S, R^1 = H, Me, Et, Pr, Bu, R^2 = H, Me, Pr, Bu, R^3 = C$_6$H$_{11}$, Ph, 3-MeC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 2,3-Cl$_2$C$_6$H$_3$, 3,5-Cl$_2$C$_6$H$_3$, 3-F$_3$CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 2-O$_2$NC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 2-furyl, 2,1,3-bensoxadiazol-4-yl, R^4 = Me, *i*-Pr.

Sometimes solution of iodine in acetic acid [87] or sulfur [32] are applied as oxidant.

Like barbituric acids, 6-aminouracils and their 2-thioanalogs can add to activated olefins affording fused heterocyclic systems. Thus, reactions of arylmethyl-enemalononitriles [89] or of 3-aryl-2-acylacrylic acids esters [90–93] obtained by Michael condensation of aromatic aldehydes with malononitrile or 2-acetyl-acrylic acid esters result respectively in 7-amino-5-aryl-2,4-dioxo-1,2,3,4-tetrahydropyrido-[2,3-*d*]pyr-imidine-5-carbonitriles (**58**) in 60–90% yield and 5-aryl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]-pyr-imidine-5-carboxylic acids esters (**59**). Compounds of (**59**) type form also at three-component condensation of 1,3-dimethyl-6-aminouracils, or 2,6-diamino-pyrimidin-4(3*H*)-one, benzoylacetic acids esters, and aromatic aldehydes [94]. Sometimes the combination of Michael condensation with reaction of aminohydroxy-pyrimidine with α,β-unsaturated carbonyl compounds resulted in considerable
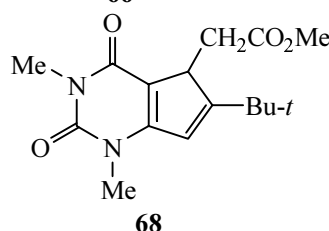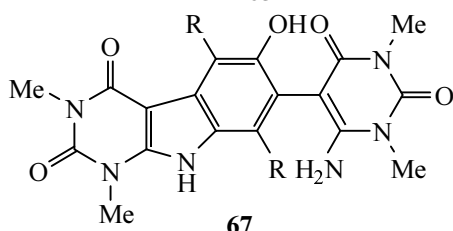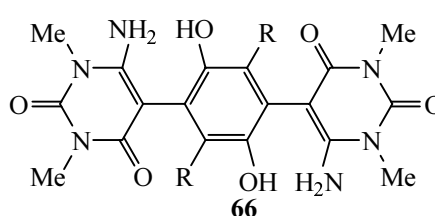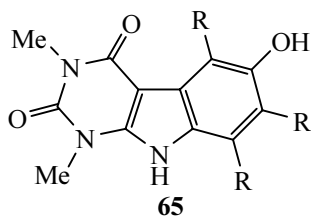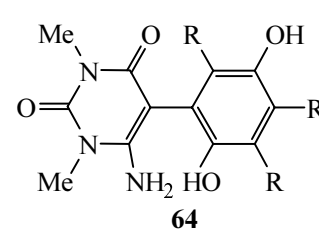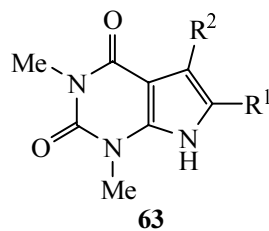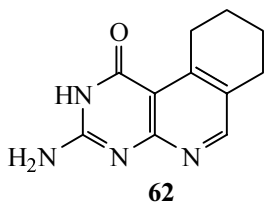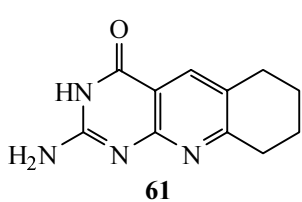
reduction of the yield of pyrido-[2,3-*d*]-pyrimidine derivatives [91].

By an example of alkyl-7-alkyl-2,4-dioxo-5-(4-fluorophenyl)-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-5-carboxylates (**59**) was demonstrated their successful oxidation into alkyl-7-alkyl-2,4-dioxo-5-(4-fluorophenyl)-1,2,3,4-tetrahydropyrido[2,3-*d*]-pyrimidine-5-carboxylate effected by diluted nitric acid [91] or by 2,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,4-dicarbonitrile [92].

6-Aminouracil and 1-cyclohexenecarbaldehyde heated in 20% hydrochloric acid are exclusively converted into 7,8,9,10-tetrahydropyrimido[4,5-*c*]isoquinoline-1,3(2*H*,4*H*)-dione (**60**), a tricyclic system of an angular structure [95].

60
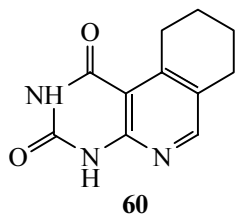
Heating 2,6-diaminopyrimidine-4(3*H*)-one with 1-cyclohexenecarbaldehyde in acetic acid resulted in a mixture of tricyclic compounds of linear and angular structure: 2-amino-6,7,8,9-tetrahydropyrimido[4,5-*b*]-quinolin-4(3*H*)-one (**61**) and 3-amino-7,8,9,10-tetrahydropyrimido[4,5-*c*]isoquinolin-1(2*H*)-one (**62**)

[95]. In this case condensation of reagents occurs in two possible directions.

The condensation of hydroxypyrimidine with α,β-unsaturated carbonyl compound is sometimes preceded by dimerization of the latter (by Michael reaction) [32, 87]. These dimmers in their turn condense with 6-amino-pyrimidin-4(3*H*)-ones. For instance, from 6-amino-1,3-dimethyluracil and 4-phenyl-3-buten-2-one in ethanol in the presence of sodium ethylate or in trifluoroacetic acid 1,3,6-trimethyl-5,8-diphenyl-8,9-dihydropyrimido-[4,5-*b*]-quinoline-2,4(1*H*,3*H*)-dione was obtained in a low yield (12–22%) [32]. The latter on heating with sulfur suffered dehydrogenation into 1,3,6-trimethyl-5,8-diphenyl-pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione.

In condensation of 6-amino-1,3-dimethyluracil with 3-hexene-2,5-dione and 1,4-diphenyl-2-butene-1,4-dione in the boiling acetic acid the carbonyl group and the carbon atom in the α-position of the latter are involved. Here the derivatives of 1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione are obtained (**63**) [96]. In reaction of 6-amino-1,3-dimethyluracil with *p*-benzoquinone and chloranil in acetic acid or nitromethane substituted hydroquinones (**64**) first arise that either undergo cyclization into indolopyrimidines (**65**) or are oxidized into substituted quinones under the reaction conditions. The latter react with additional molecule of pyrimidine and convert into 2,5-bis(pyrimidine-5-yl)-hydroquinones (**66**) [30, 97]. The reactoin mixtures contain all three compounds (**64**–**66**). Pfleiderer and Grozinger [30]

61   **62**   **63**   **64**

65   **66**

67   **68**

63, R^1 = Me, Ph, R^2 = AcCH$_2$, PhCOCH$_2$; **64**–**67**, R = H, Cl.

gescribed the conversion of hydroquinones (**66**) into 7-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-6-hydroxy-1,3-dimethyl-1*H*-pyrimido-[4,5-*b*]indole-2,4(3*H*,9*H*)-diones (**67**).


69, **70**, **71**, **72**, **73**, **74**
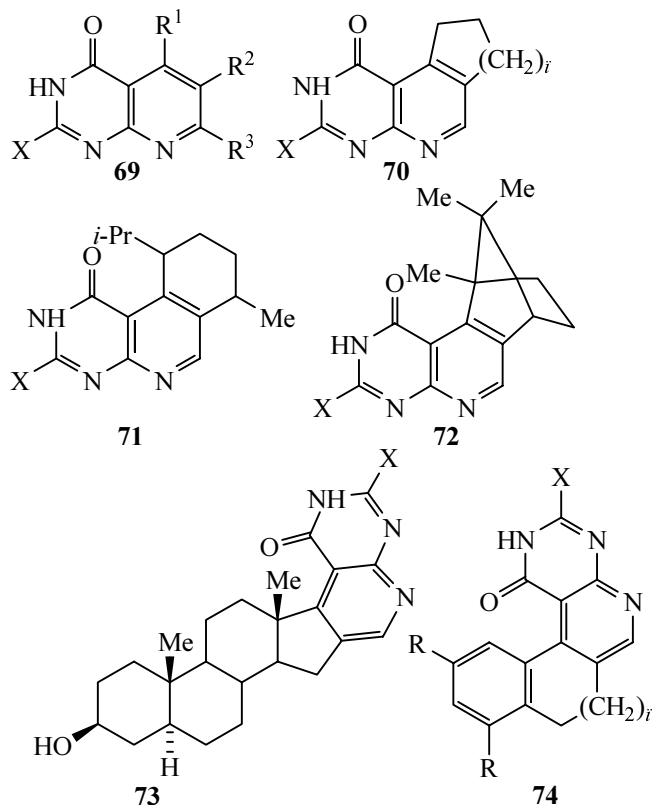
69–**71**, **73**, **74**, X = OH, SH, NH$_2$; **72**, X = SH, NH$_2$; **69**, R^1 = H, Me, Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, R^2 = H, Me, Pr, Bu, C$_5$H$_{11}$, R^3 = H, Me; **70**, n = 1–4, 8; **74**, R = H, Me; n = 0, 1.

When methyl 5,5-dimethyl-4-oxo-2-hexanoate was used in this reaction as the carbonyl component (in boiling ethanol) a derivative of 1*H*-pyrrolo[2,3-*d*]-pyrimidine (**68**) was obtained in 14% yield [98].

Yet when during the condensation of 6-amino-1,3-dimethyluracil with 3-hexene-2,5-dione and 1,4-diphenyl-2-butene-1,4-dione in boiling pyridine a flow of oxygen was passed through the reaction mixture derivatives of pyrido-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**51**, X = O, R^1 = Me, R^2 = Ac, PhCO, R^3 = H, R^4 = Me, Ph) formed in 37–48% yield[96]. The reaction between 6-amino-1,3-dimethyluracil with unsymmetrical methyl 5,5-dimethyl-4-oxo-2-hexanoate carried out under these conditions occurred through coordination of the keto group of the latter with the amino group of the aminouracil.

Therewith methyl 7-*tert*-butyl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylate was obtained in 36% yield [98].

75
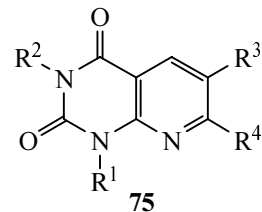
R^1 = Me, Et, R^2 = H, Me, R^3 = H, Me, R^4 = 3-O$_2$NC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 4-ClC$_6$H$_4$, CH=CHPh, 2-thienyl, 3-indolyl.

76   **77**
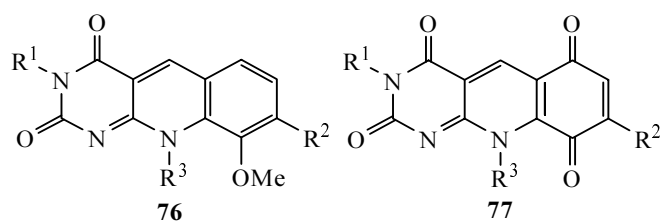
R^1 = H, Me, Ph, R^2 = H, Me, R^3 = Bu, C$_6$H$_{13}$, C$_8$H$_{17}$, C$_{12}$H$_{25}$.

6-(Dimethylaminomethyleneamino)-1,3-dimethyluracil heated in toluene with 3-buten-2-one (methyl vinyl ketone) afforded in 62% yield 6-acetyl-1,3-dimethyl-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione; the reaction occurred with dimethylamine elimination. The reaction product by dehydrogenation with nitrobenzene was converted into 6-acetyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione [17, 99].

78   **79**
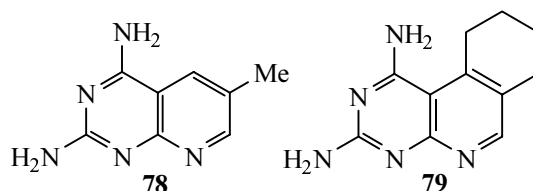
In the process of 6-aminouracil, 6-amino-2-thiouracil, or 2,6-diaminopyrimidin-4(3*H*)-one condensation with α,β-unsaturated β-aminoaldehydes or ketones (aliphatic [100–102], alicyclic [100, 102], among them terpenoid [100] and steroid [82, 103]), the carbonyl group of the latter coordinated to the C^5 atom of the pyrimidine, and a single type of reaction products formed, pyrido[2,3-*d*]-pyrimidin-4(3*H*)-one derivatives (**69**–**74**).

The condensation of 6-aminouracils and 6-amino-2-thiouracils with α,β-unsaturated β-aminocarbonyl compounds in a mixture of acetic acid with water **80**,

80   **81**
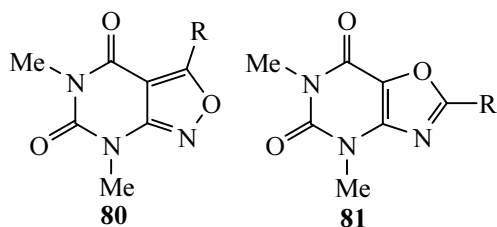
R = Ph, 4-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$; **81**, R = Ph, 4-BrC$_6$H$_4$.

occurred with replacement of the β-amino group like the reactions with the β-haloanalogs of the latter described above. Here also the pyrido[2,3-*d*]pyrimidine system (**51**) is generated [100]. α,β-Unsaturated β-aminocarbonyl compounds from acyclic and terpene series provide in these reactions compounds (**70–74**, X = NH) [100].

At heating 6-aminouracils with β-dimethylamino-ketones hydrochlorides in boiling acetic acid the derivatives of pyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**75**) were obtained [40]. The reaction should involve the oxidation of the intermediate products.

The condensation of 6-aminouracils with 2,3-di-methoxy- and 2,3,4-trimethoxybenzaldehydes in DMF resulted in 9-methoxy-5-deazaflavins (**76**) in 58–85% yield. The latter compounds were oxidized with cerium ammonium nitrate into 5-deazaflavo-6,9-quinones (**77**) [104].

III. PYRIMIDINE-2,4,6-TRIAMINES

Pyrimidine-2,4,6-triamine reacts with α,β-unsaturated aldehydes like 6-aminouracil. For instance, pyrimidine-2,4,6-triamine with 3-amino-2-methylpropenal afforded

82
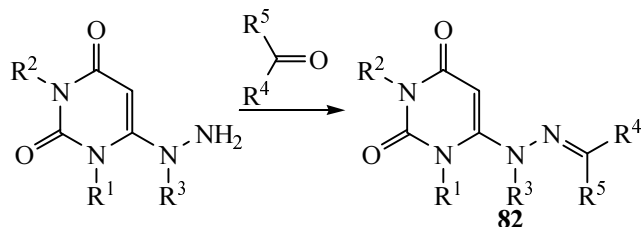
R^1 = H, Me, Ph, R^2 = H, Me, R^3 = H, Me, Et, R^4 = Me, Et, Pr, C$_5$H$_{11}$, C$_6$H$_{13}$, CH$_2$Ph, COOH, MeCH=CH, CH$_2$CH$_2$CO$_2$Me, Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 4-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 3,4-(CH$_2$O$_2$)C$_6$H$_3$, 4-Me$_2$NC$_6$H$_4$, 4-(ClCH$_2$CH$_2$)$_2$NC$_6$H$_4$, PhCH=CH, 5-nitro-2-furyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thienyl, R^5 = H, Me, Et, Pr, Ph, R^4,R^5 = (CH$_2$)$_4$, 2-oxo-1,2- dihydro-3*H*-indol-3-ylidene.

6-methylpyrido[2,3-*d*]pyrimidine-2,4-diamine(**78**), and with 1-cyclohexenecarbaldehyde gave 8,9,10-tetrahydro-pyrimido[4,5-*c*]isoquinoline-1,3-diamine (**79**) [95]. The same product was obtained in reaction with 2-chloro-1-cyclohexenecarbaldehyde. Note therewith that the latter gave with 6-aminouracil and also with 2,6-diamino-pyrimidine-4(3*H*)-one tricyclic products of the linear structure [95]. Thus the structure of the hydroxy-(amino)-pyrimidine essentially affects the direction of condensation with α,β-unsaturated β-halocarbonyl compounds.

83

84   **85**

86   **87**
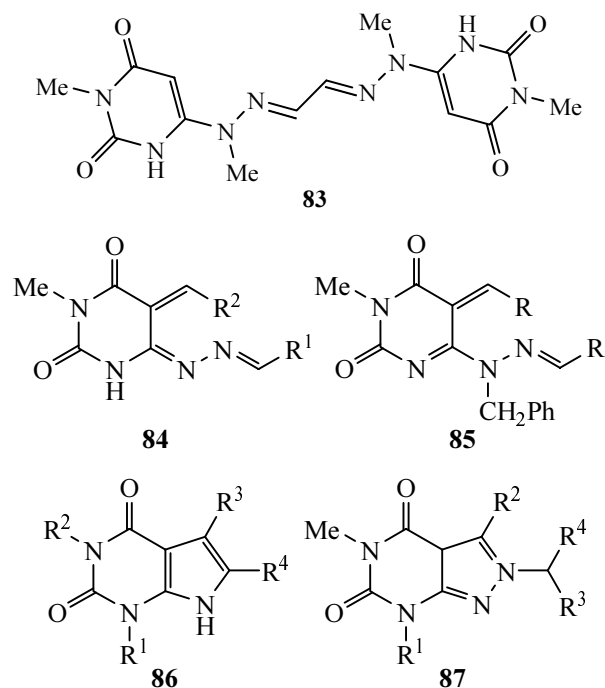
84, R^1 = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, R^2 = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$; **85**, R = Ph, 2-furyl. **86**, R^1 = Me, Et, C$_8$H$_{17}$, CH$_2$Ph, CH$_2$CH$_2$CN, Ph, R^2 = Me, Et, C$_8$H$_{17}$, CH$_2$Ph, CH$_2$CH$_2$CN, Ph, R^3 = Cl, CN, CONHR, SO$_2$NHR, Ph, Ar, R^4 = H, Cl, SAr, SHt; **87**, R^1 = H, Me, R^2 = Ph, 4-ClC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 4-MeOC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, R^3 = MeCH=CH, Ph, 4-ClC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 4-MeOC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, PhCH=CH, R^4 = H, Me.

IV. 6-(HYDROXYIMINO)URACILS

During the condensation of 6-hydroxyimino-1,3-dimethyluracil with aromatic aldehydes in boiling DMF occurred an oxidative cyclization of 5-arylmethylene derivatives apparently arising intermediately. As a result 3-aryl-5,7-dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones (**80**) were obtained in 29–65% yield [105]. The latter under UV irradiation of their alcohol

solutions underwent a rearrangement into 2-aryl-4,6-dimethyl[1,3]oxazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**81**) [105].

Like 6-aminouracil, 6-(hydroxyimino)-uracils can add to activated olefins to provide fused heterocyclic systems. For instance, 7-amino-5-aryl-6-cyano derivatives of pyrido[2,3-*d*]pyrimidine (**58**) were obtained in reaction with arylmethylenemalononitriles in 60–85% yield [89].

88
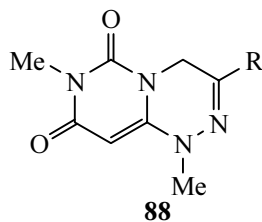
R = Ph, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$.

V. 6-HYDRAZINOURACILS

In reactions of 6-hydrazinouracils with carbonyl compounds, including monosaccharides (*D*- and *L*-arabinose, *D*-glucose, *D*-mannose, *D*-galactose, *D*-fructose, *D*-glucuronolactone, *D,L*-glyceraldehyde and glycolaldehyde) [106] form first of all not condensation products at the C^5 atom of the pyrimidine ring, but the corresponding hydrazones (**82**) in 41–97% yield [39, 107–113]. The solvents used here are methanol, ethanol, and xylenes.

89   **90**
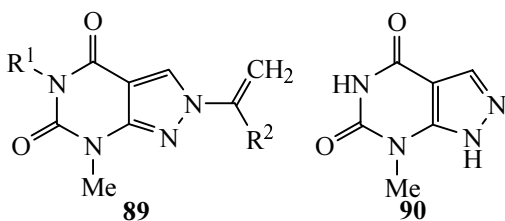
R^1 = H, Me, Et, *i*-Pr, R^2 = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$.

3-Methyl-6-(1-methylhydrazino)uracil with glyoxal gave as a minor product bishydrazone (**83**) (yield 20%) [78].

91   **92**
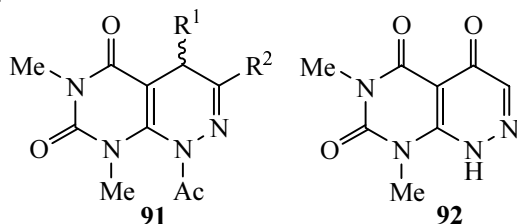
R^1 = (CHOAc)$_2$CH$_2$OAc, (CHOAc)$_3$CH$_2$OAc, R^2 = H, CH$_2$OAc.

Heating of 6-(2-arylmethylenehydrazino)-3-methyluracils with aromatic aldehydes in ethanol under relatively mild conditions resulted in isolation of 5-aryl-methylene derivatives (**84**) [108, 114] or (**85**) [109].

Hydrazones (**82**) at heating undergo a cyclization into 1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-(3*H*,7*H*)-dione derivatives (**86**) [115].

Compounds (**84**) heated in DMF afford 2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione derivatives (**87**, R^1 = H) [108, 114].

Compounds (**87**) may be prepared leaving out the isolation of 5-arylmethylene derivatives (**84**) by heating a mixture of hydrazones (**82**) with aromatic aldehydes in DMF. Thus from hydrazones (**82**, R^1 = H, Me, R^2 = Me, R^3 = R^5 = H) and aromatic aldehydes were prepared derivatives of 2*H*-pyrazolo-[3,4-*d*]pyrimidine-4,6-(5*H*,7*H*)-dione (**87**) in 32–87% yield [108, 114].

93   **94**
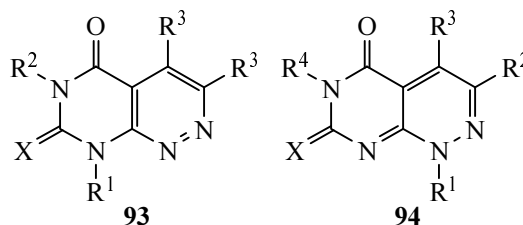
R^1 = (CHOAc)$_2$CH$_2$OAc, (CHOAc)$_3$CH$_2$OAc, R^2 = H, CH$_2$OAc.

The carbonyl group of α-halocarbonyl compounds also coordinates to the hydrazine group of the 6-hydrazino-uracil. The presence of a halogen atom in the α-position of the carbonyl component favors a formation of a 6-membered ring, either pyridazine one at the cost of the C^5 atom or 1,2,4-triazine ring involving the N^1 atom of pyrimidine. For instance, long heating of 3-methyl-6-(1-methylhydrazino)uracils with α-bromoacetophenones in boiling ethanol gave rise to 4-deatoxoflavins (**94**) in 28–43% yield alongside derivatives of 4*H*-pyrimido[6,1-*c*]-[1,2,4]triazine-6,8(1*H*,7*H*)-diones (**88**) [116].
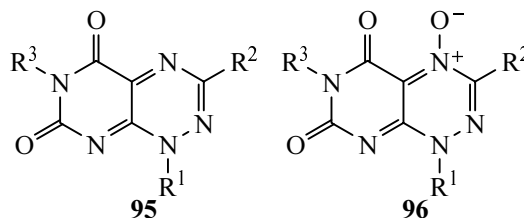
95   **96**

95, 96, R^1 = Me, Et, CH$_2$Ph, R^2 = H, Me, Ph, 4-ClC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 4-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 3,4-(CH$_2$O$_2$)C$_6$H$_3$, 4-Me$_2$NC$_6$H$_4$, PhCH=CH, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thienyl, R^3 = Me, Ph.

At heating hydrazones (**82**, R^1 = Me, R^2 = H, R^4 = Me, R^5 = Ar) with dimethylformamide dialkylacetals derivatives of 2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**89**) were obtained [111]. Thus not only pyrazole ring closure occurred , but also the N^3 atom of the pyrimidine ring suffered alkylation. The same compounds can be converted into 7-methyl-1*H*-pyrazolo[3,4-pyrimidine-4,6(5*H*)-dione (**90**) in an overall yield ~50% by treating in succession with dimethylformamide dimethylacetal and trichloracetic, trifluoroacetic, or hydrochloric acid. The intermediate substances in this process are 5-dimethylaminomethylene derivatives of hydrazones (**82**) that build up the pyrazole ring in the presence of acids with liberation of the corresponding acetophenones and dimethylamine.


97

98
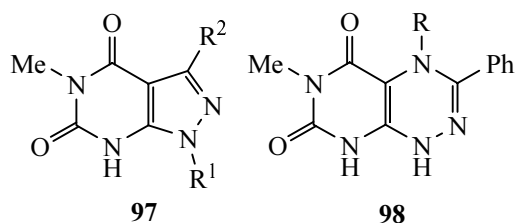
97, R^1 = Et, CH$_2$Ph, R^2 = 4-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 4-Me$_2$NC$_6$H$_4$, 2-furyl; **98**, R = H, CHO.

Hydrazones (**82**) formed from pentoses and hexoses, and also from *D*-fructose and *D*-glucuronolactone are converted in acetic anhydride containing pyridine into derivatives of 4,8-dihydropyrimido[4, 5-*c*]pyridazine-5,7(1*H*,6*H*)-dione (**91**) [106]. The acetoxy groups of the latter are easily deacylated by ammonia solution in methanol.

Yet hydrazones (**82**) prepared from glyceraldehydes or glycolaldehyde at treatment with acetic anhydride containing pyridine undergo only acetylation of the hydroxy groups and not cyclization [106].

The reaction of 1,3-dimethyl-6-hydrazinouracil with glyoxylic acid did not stop at the stage of hydrazone formation, and the following transformations resulted in 6,8-dimethylpyrimido[4,5-*c*]pyridazine-4,5,7-(1*H*,6*H*,8*H*)-trione (**92**) [112].

The pyridazine ring fused to that of pyrimidine is also built up in reactions of 6-hydrazinouracils with α-dicarbonyl compounds. For instance, 6-hydrazinouracils and 2-amino-6-hydrazinopyrimidin-4(3*H*)-ones, both methylated and nonmethylated in positions *1* and *3*, in reactions with 2,3-butanedione, 9,10-phenanthrenedione, acenaphthoquinone, and benzil proceeding in acetic acid are converted into the corresponding derivatives of

99

100
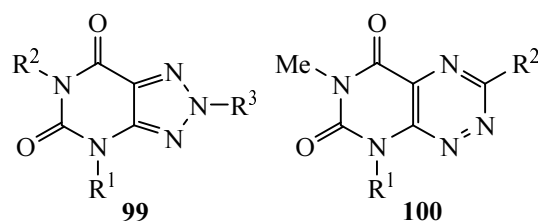
99, R^1 = Me, R^2 = Me, R^3 = isopropenyl, 1-methyl-propenyl, 1-phenylvinyl, 1-(4-methylphenyl)-vinyl, 1-(4-chlorophenyl)vinyl; **100**, R^1 = H, Me, R^2 = H, Me, Ph, 4-ClC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 4-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 3,4-(CH$_2$O$_2$)C$_6$H$_3$, 4-Me$_2$NC$_6$H$_4$, PhCH=CH, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thienyl.

pyrimido[4,5-*c*]pyridazine (**93**) [78, 107]. 6-(1-R-Hydrazino)uracils heated in acetic acid, DMF, or ethanol with glyoxal, 2,3-butanedioneom, benzil, and other α-diketones give the corresponding substituted pyrimido[4,5-*c*]-pyridazine-5,7(1*H*,6*H*)-diones (**94**) in 48–100% yield [78, 117].
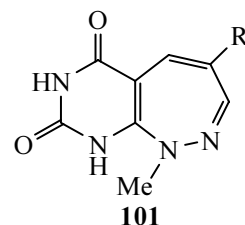
101

R = Me, Et, *i*-Pr, Bu.

Compounds (**94**), as remote analogs of riboflavin, are fairly readily reduced to 4,8-dihydro derivatives with Na$_2$S$_2$O$_4$ or primary amines whereas the latter are oxidized to aldehydes [117].

6-Hydrazinouracil, 3-methyl-6-(1-methylhydrazino)-uracil, and 6-hydrazino-1,3-dimethyluracil with isatin form only the corresponding hydrazones (**82**) involving the CO group in the *3* position of the latter [107].
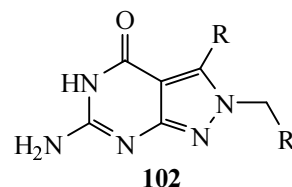
102

R = Ph, 4-ClC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 4-MeOC$_6$H$_4$.

Ketone hydrazones (**82**) at heating in ethylene glycol or tetralin eliminate ammonia and convert into derivatives of 1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**28**) in 13–95% yield [39].

Compounds (**94**) were obtained at prolonged heating of 6-(2-arylmethylene-1-methylhydrazino)-3-methyl-uracils (**82**) with triethyl orthoformate in DMF at 160°C in 30–43% yield [116].

Hydrazones (**82**) treated with $NaNO_2$ in acetic acid at 20°C furnish toxoflavins (**95**) in 30–87% yield [109, 118], or toxoflavin-4-oxides (**96**) in 20–79% yield, or their mixtures [110, 118]. Mixtures of the same substances were obtained in lower yields applying for the cyclization a system KNO_3–H_2SO_4–AcOH [110].

103

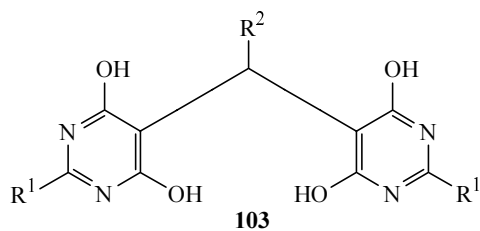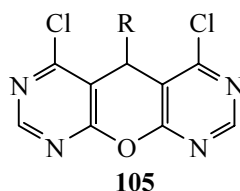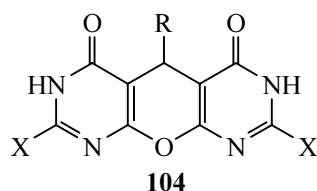R^1 = H, Me, MeS, NH_2, R^2 = H, Me, Pr, *i*-Bu, C_7H_{15}, Ph, 4-$Me_2NC_6H_4$, 4-$O_2NC_6H_4$, 4-HOC_6H_4, 4-$MeOC_6H_4$.

104　　　　　　　　**105**

X = H, Me, SMe, NH_2, R = H, Me, Pr, *i*-Bu, C_7H_{15}, Ph, 4-$Me_2NC_6H_4$, 4-$O_2NC_6H_4$, 4-HOC_6H_4, 4-$MeOC_6H_4$.

This reaction carried out in boiling acetic acid afforded 1*H*-pyrazolo-[3,4-*d*]pyrimidine-4,6(5*H*)-dione derivatives (**97**) [109].

Sodium dithionite ($Na_2S_2O_4$) reduces the toxoflavin-4-oxides (**96**) to the corresponding 4,8-dihydro derivatives [110].

Only toxoflavins (**95**) were obtained in 35–67% yield from hydrazones (**82**) and isopentyl nitrite in ethanol [118].

106　　　　　　　　**107**
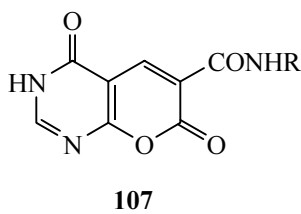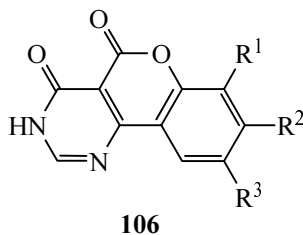
106, R^1 = H, OH, MeO, Br, Cl, R^2 = H, OH, R^3 = H, Br, Cl, NO_2; **107**, R = H, CHO.

3-Phenyl derivatives (**95**, **96**) were reduced with $Na_2S_2O_4$ to 4,8-dihydro derivative (**98**, R = H) in 72% yield, and the latter easily converted in air into the initial toxoflavin (**95**). In the reaction with $Na_2S_2O_4$ carried out in formic acid toxoflavin (**95**, R = Ph) reduction is combined with its formylation in position *4* [118]. At heating compounds (**95**, **96**) in DMF, dimethylacetamide, or in acetic acid they suffer demethylation to afford 1-demethyltoxoflavins (**100**, R^1 = H) in 72–97% yield [118].

108
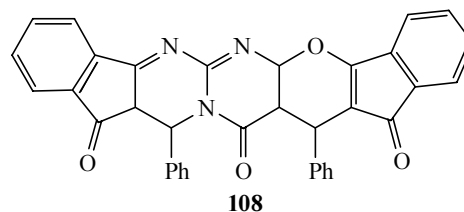
At heating a mixture of ketone hydrazones (**82**), *N*-nitrosodimethylamine, and $POCl_3$ form derivatives of 2*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7-(4*H*,6*H*)-diones (**99**) in 31–65% yield [113]. Under the same conditions the 6-benzylidenehydrazino-1,3-dimethyluracil was converted into 3-phenylfervenulin (**100**) [113].

6-Hydrazinouracil heated with 3-amino-(ethoxy)-2-methylacrylaldehyde in acetic acid is converted into 6-(4-methylpyrazol-1-yl)-uracil in 62% yield [119]. Yet the products of a similar reaction between 6-(1-methyl-hydrazino)-uracil and 2-R-3-amino(ethoxy)acryl-aldehydes are 1*H*-pyrimido[4,5-*c*][1,2]diazepine-6,8-(7*H*,9*H*)-dione (**101**) (yield 35–59%) [119]. When carbonyl component had no substituent in position *2* the reaction products were not identified.

VI. 2-AMINO-4-HYDRAZINO-6-HYDROXYPYRIMIDINES

At heating in DMF the 2-amino-6-(2-arylmethyl-enehydrazino)pyrimidin-4(3*H*)-ones undergo cyclization into 6-amino-2,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones (**102**) that can be also prepared under these conditions from 2-amino-6-hydrazinopyrimidin-4(3*H*)-one and excess aromatic aldehyde [108].

VII. 4,6-DIHYDROXYPYRIMIDINES

4,6-Dihydroxypyrimidine and its 2-substituted derivatives with benzaldehyde [120], aliphatic and aromatic aldehydes in water, pyridine, and acetic acid give 5,5'-ylidenebis(4,6-dihydroxypyrimidines) (**103**) in 80–95% yield [121–126].

Heating the latter in a mixture of acetic acid and its anhydride or in $POCl_3$ in the presence of *N,N*-diethyl-

aniline affords derivatives of 5,7-dihydro-4*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-4,6(3*H*)-dione (**104**) or 4,6-dichloro-5*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine (**105**) respectively [121–126].

In reaction of 4,6-dihydroxypyrimidine with salicylaldehyde and its substituted derivatives alongside bispyrimidines (**103**) were isolated coumarin-3-carboxamides, their N-formyl derivatives, and 4*H*-chromeno-[4,3-*d*]pyrimidine-4,5(3*H*)-diones (**106**). The formation of the latter three compounds should have occurred with the opening of the pyrimidine ring [127]. The condensation of 4,6-dihydroxypyrimidine with 4,6-dihydroxypyrimidine-5-carbaldehyde also involved the opening of the pyrimidine ring. Therewith arise 4,7dioxo-3,7-dihydro-4*H*-pyrano[2,3-*d*]pyrimidine-6-carboxamides or N-formyl derivatives thereof (**107**) [128].

The condensation of 2-amino-4,6-dihydroxy-pyrimidine with 2-benzylidene-1*H*-indene-1,3(2*H*)-dione at heating the reagents in the presence of 4-methyl-benzenesulfonic acid gave in 55% yield diindenopyrano-pyrimidopyrimidine (**108**) whose molecule combined the reactant in the ratio 1:2 [129]. Like in reactions of 6-aminouracils with α,β-unsaturated carbonyl compounds the C^5 atom of pyrimidine attacks the β-position of the carbonyl compound.

VIII. CONCLUSION

It is evident from the review that the reactions of hydroxy- and aminopyrimidines with versatile carbonyl compounds, also those involving a third component, open up wide and not yet exhausted opportunities for syntheses of pyrimidine-containing heterocyclic systems. Therewith apparently succeed preparations of compounds with molecules both containing a pyrimidine ring isolated from the other heterocyclic fragments with nitrogen, oxygen, sulfur, and selenium atoms, and also where these heterocycles are fused to pyrimidine ring. It should be noted also that all the diversity of the chemical transformations and products obtained mentioned in publications was achieved with the use of relatively limited number of types of pyrimidine and carbonyl componentsенто. Nonetheless, even this rather scarce set of reactants is quite sufficient for successful search for new compounds with useful properties among the condensation products of hydroxypyrimidines with carbonyl compounds or their analogs.

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