SYNTHESIS OF 3-SUBSTITUTED 4-METHYLMERCAPTO- AND 4-AMINOPYRAZOLO-
[3,4-d]PYRIDINES AND THEIR RIBOSIDES

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3-Cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine, fusion of which with 1,2,3,5-
tetra-O-acetyl-β-D-ribofuranose gave its per-O-acetylated β-D-ribofuranoside in
61% yield, was synthesized from 3,4-dicyano-5-aminopyrazole. O-Deacetylation of
the per-O-acetylated β-D-ribofuranoside was carried out by the action of 1% HCl
in methanol. New pyrazolo[3,4-d]pyrimidines were obtained by the reaction of
3-cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine and its 1-riboside, as well as
3-cyano-4-aminopyrazolo[3,4-d]pyrimidine, with a number of nucleophilic reagents.
The cytotoxic activities of the compounds obtained were studied.

The high cytotoxic activities of 4-aminopyrazolo[3,4-d]pyrimidine and its β-D-ribo-
furanoside are known [1]. β-D-Ribofuranosides of 3-substituted 4-aminopyrazolo[3,4-d]-
pyrimidines also have pronounced cytotoxic activity [2]. Nucleosides of 3,4-disubstituted
pyrazolo[3,4-d]pyrimidines with substituents other than an amino group in the 4 position
have not been described. The preparation of 3-substituted pyrazolo[3,4-d]pyrimidines and
the corresponding nucleosides with a methylmercapto group in the 4 position, which is
capable of imitating an amino group in several enzymatic processes, seems of interest.

We accomplished the synthesis of 3-substituted 4-methylmercaptopyrazolo[3,4-d]pyrimi-
dines from 3,4-dicyano-5-aminopyrazole (I), which was obtained from malononitrile by a known
four-step synthesis [3]. 3-Cyano-4-mercaptopyrazolo[3,4-d]pyrimidine (III) was obtained in
78% yield on the basis of starting pyrazole I when I was heated in excess ethyl orthoformate
[4], without isolation and purification of the intermediate 3,4-dicyano-5-ethoxymethylene-
aminopyrazole (II), with subsequent condensation with sodium hydrosulfide in absolute meth-
anol [5] and treatment of the reaction product with alkali. Methylation of pyrazolopyrimidine
III with methyl iodide in NaOH gave 3-cyano 4-methylmercaptopyrazolo[3,4-d]pyrimidine
(IV) in 89% yield; the latter was subsequently used in reactions with nucleophilic reagents
and to obtain nucleosides.

3-Thiocarbamoyl-4-methylmercaptopyrazolo[3,4-d]pyrimidine (V) was obtained in 50% yield
when dry hydrogen sulfide was passed through a solution of IV in absolute ethanol containing
triethylamine. The reaction of IV with hydrazine hydrate in ethanol led to 4-hydrazinopyra-
zolo[3,4-d]pyrimidine-3-carboxylic acid iminohydrazone (VI) in 60% yield.

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The previously undescribed 3-thiocarbamoyl-4-aminopyrazolo[3,4-d]pyrimidine (VIII) and 4-aminopyrazolo[3,4-d]pyrimidine-3-carboxylic acid amidoxime or iminohydrazide (IX or X) — aglycones of the corresponding L-ribosides, which have pronounced anticancer activity [2] — were synthesized in 50-70% yields as a result of nucleophilic addition of hydrogen sulfide, hydroxylamine, or hydrazine hydrate to the nitrile group of 3-cyano-4-aminopyrazolo[3,4-d]pyrimidine (III), which we obtained from pyrazole I by the method in [6]. For the glycosylation of 3-cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine IV we selected the method of fusion in the presence of iodine, by which L-ribosides of 3-cyano- and 3-cyano-methyl-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidines were previously obtained [7, 8].

1-(2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)-3-cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine (XII) was obtained in 61% yield by fusing IV with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (XI) in vacuo in the presence of 12% iodine at 165°C. In addition, 2-8 isomer XIII was isolated in very low yield (~3%).

The O-deacetylation of XII by the action of a 1% solution of hydrogen chloride in absolute methanol [9] led to 1-(β-D-ribofuranosyl)-3-cyano-4-methylmercaptopyrazolo[3,4-d]pyrimidine (XIV) in 62% yield. We were unable to remove the O-acetyl groups by such widely used (in the chemistry of nucleosides) methods as the action of a methanol solution of ammonia or sodium methoxide in methanol without involvement of the nitrile group.

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The structures of nucleosides XII and XIV were confirmed by conversion of riboside XII to a nucleoside with known structure XVII. 1-(2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)-3-thiocarbamoyl-4-methylmercaptopyrazolo[3,4-d]pyrimidine (XV) was formed in 53% yield when hydrogen sulfide was passed through a solution of riboside XII in ethanol in the presence of triethylamine. 1-(β-D-Ribofuranosyl)-3-thiocarbamoyl-4-methylmercaptopyrazolo[3,4-d]pyrimidine (XVI) was obtained in 75% yield when XV was deacetylated with sodium methoxide in absolute methanol. Ammonolysis of riboside XV with a saturated methanol solution of ammonia in an ampul at 100°C led to 1-(β-D-ribofuranosyl)-3-thiocarbamoyl-4-aminopyrazolo-[3,4-d]pyrimidine (XVII), which, according to the UV spectral data and the specific optical rotation, was identical to the previously described compound [10, 11].

The structure of 2-riboside XIII was confirmed by UV spectral data. Heterocycle IV and 1-nucleosides XII and XIV have similar UV spectra (Fig. 1). The UV spectrum of riboside XIII differs substantially from them; this constitutes evidence for a different type of substitution of the heterocyclic ring and makes it possible to assign the 2-isomer structure to riboside XIII.

The assumption that riboside XIII is the 5 or 7 isomer seems unlikely to us, since the formation of only 1- and 2-ribosides was previously observed in the glycosylation of 4-methylmercaptopo- and 4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidines by the fusion method [12, 13].