ALKYLATION AND REDUCTIVE DETHIATION OF 2-THIOXO- AND 1,2,3,4-
TETRAHYDROPYRIMIDINE-5-CARBOXYLIC ACID DERIVATIVES


2-Methylthio-1,4-dihydropyrimidines were obtained by methylation of 2-
thioxo-4-phenyl-5-methoxycarbonyl-6-methyl-1,2,3,4-tetrahydropyrimidine
or its 1-methyl derivative in a neutral medium. The alkylation of
tetrahydropyrimidine-2-thiones in the anionic form leads to S- and S,N-
methylation products. Iodoacetamide alkylates pyrimidine-2-thione with
the formation of thiazolidino[3,2-a]pyrimidine derivatives. The reductive
dethionation of derivatives of tetrahydropyrimidine-2-thiones and
2-methylthio derivatives of 1,4- and 3,4-dihydropyrimidines was accom-
plished.

It is known [1, 2] that exclusively S-alkyl derivatives are formed in the alkylation
of 2-thioxo-1,2,3,4-tetrahydropyrimidine derivatives in a neutral medium. In the present
research we studied the alkylation of methyl 2-thioxo-4-phenyl-6-methyl-1,2,3,4-tetrahydropy-
rimidine-5-carboxylate (I) and its 1-methyl derivative II in a neutral medium and in the
presence of a strong base – sodium hydride.

The alkylation of pyrimidine-2-thiones I and II with methyl iodide in a neutral medium
leads to the formation of stable salts IIIa, b, which in an aqueous alkaline medium are
readily converted to the free bases – 2-methylthio-1,4-dihydropyrimidines IVa, b. It should
be noted that only 1,4-dihydropyrimidine IVa was isolated in the alkylation of unsubstituted
pyrimidine I; the other possible isomer – 3,4-dihydropyrimidine – is not formed under the
conditions described.

It is known that an attempt to alkylate 2-thioxo-1,2,3,4-tetrahydropyrimidine in an
aqueous alkaline medium leads only to hydrolysis of the C=S group to a carboxyl group [1].

We have observed the possibility of alkylation of pyrimidine-2-thione I in the presence
of a base – sodium hydride; the effects of the solvent [1,2-dimethoxystrene (DME) or hexa-
metapol (HMP)], the nature of the alkylating agent [methyl iodide or dimethyl sulfate (DMS)],
and the amount of base, which is responsible for the formation of the 2-thioxo-1,2,3,4-tetra-
hydropyrimidine anion, were studied.

Thus S-monoalkylation product IVa is formed in the alkylation of pyrimidine-2-thione
I in the anionic form (shift of the long-wave maximum in the UV spectrum from 308 nm to
362 nm when one equivalent of NaH is added to a solution of I), regardless of the solvent
used and the alkylating agent. A mixture of S-monoalkyl derivative IVa and dialkylation
product V, as well as a very small amount of IVb, is the result of alkylation in the pres-
ence of two equivalents of NaH. The yields of the products obtained (from the results of
liquid chromatography) in different solvents and with different alkylating agents are
presented in Table 1, from which it is apparent that S monoalkylation predominates, regardless of the reaction conditions, while an increase in the dipole moment of the solvent increases the percentage of the $S,N(3)$-dialkylation product.

3,4-Dihydropyrimidine V is the principal reaction product in the alkylation of 2-methylthio-1,4-dihydropyrimidine IVa in the presence of NaH, and its isomer IVb is formed in very small amounts ( ~9%).

On the basis of the data obtained it might be assumed that pyrimidinethione I forms anions A and B in the presence of strong bases in solutions:

The structure of anion A is confirmed by the absence in its $^1H$ NMR spectrum of a vicinal $^3J_3,4$ spin-spin coupling constant (SSCC) and by the presence of a strong-field 2 ppm shift of the 1-H signal as compared with the corresponding signal of pyrimidine I. The concentration of anion B is so low that it could not be recorded in the $^1H$ NMR spectrum. It is apparent that the alkylation of pyrimidine-2-thiones proceeds as a function of the concentrations of the anions and the distribution of the nucleophilicity in the corresponding anions.

In the $^1H$ NMR spectrum of the monoalkylation product – salt IIIa – the chemical shifts of the 1-NH and 3-NH protons are averaged and are found at weak field (10.31 ppm), on the basis of which the structure of the salt can be conceived of in the form of a cation with the charge delocalized among the $N(3)$, $S$, $N(1)$, and $C(2)$ atoms. The signal of the 4-H proton in the spectrum of IVb is located at weaker field as compared with the signal of the corresponding isomer V ( $\delta$ 0.57 ppm), while the positions of the signals of the N-CH$_3$ group of these compounds differ by 0.22 ppm. According to the $^{15}N$ NMR spectral data, the $N(3)$ atom in IVb has sp$^2$ hybridization, whereas in isomer V it has sp$^3$-hybrid character. The assignment of the signals in the $^{15}N$ NMR spectrum was made on the basis of a study of the corresponding spectrum of starting pyrimidine I, in which the signal of the $N(1)$ atom in the form of a multiplet has $\delta$ -235.69 ppm ($J_{\text{IsNH}} = 96.4$ Hz), while the signal of the $N(3)$ atom in the form of a doublet has $\delta$ -253.74 ppm ($J_{\text{IsNH}} = 96.1$ Hz).

A thiazolidine ring with the participation of the nitrogen atom of the pyrimidine ring is formed in the alkylation of unsubstituted pyrimidinethione I with iodoacetamide. The chemical shift of the 4-H signal in the $^1H$ NMR spectrum of the cyclization product to weak field (6.02 ppm) makes it possible to assume that the $N(3)$ atom has sp$^2$ hybridization, and consequently, the formation of thiazolidine ring VI with the participation of the $N(1)$ atom occurs. If the alkylation is carried out in solution in acetone, condensation product VII is isolated. 8-Benzylidene derivative VIII of the thiazolidinopyrimidine is also readily formed in the reaction of VI with benzaldehyde.

The reductive dethionation of pyrimidines I, II, and IVa, b with Raney nickel results in the formation of 1,4-dihydropyrimidines IXa, b. According to the $^1H$ and $^{13}C$ NMR spectral data, IXa exists in the 1,4-dihydro form. However, proton exchange between the nitrogen atoms was observed in the $^{15}N$ NMR spectra; this constitutes evidence for the existence of a tautomeric equilibrium between the 1,4- and 3,4-dihydro forms.