CHAPTER II

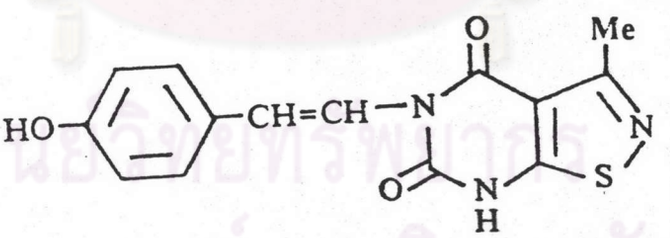
HISTORICAL

Biological Activity of Isothiazolopyrimidine Derivatives

Isothiazolopyrimidine derivatives have been found to possess many interesting biological activities as mentioned above. Followings are some details of them.

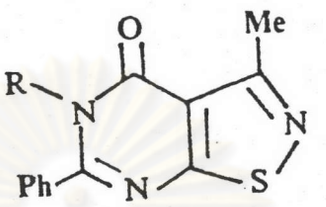
1. Oncostatic activity

5-(4′-hydroxybenzylideneimino)-4,6-diketo-4,5,6,7-tetrahydropyrimidine [4,5-d]-3-methylisothiazole (II) exerted a significant effect against leukemia, melanoma B-16, Ehrlich carcinoma, and Nometh-Kellmer lymphoma (13).



(II)

Isothiazolopyrimidine (III) show some cytotoxic effect in tumor cell (7).



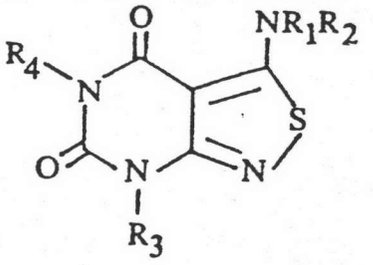
(III)

2. Antiviral activity

Isothiazolopyrimidine (III) have been reported to possess potent antiviral activity (7).

3. Sedative activity

3-(Disubstituted) aminoisothiazolo [3,4-d] pyrimidines (IV) have been reported to be useful as sedative (8).



(IV)

R_1 = Me, $HOCH_2CH_2$, Et

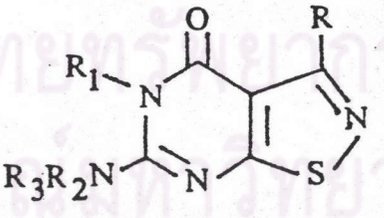
R_2 = Me, $HOCH_2CH_2$, Et, p-ClC_5H_4, Ph

R_3 = Et, Me_2CHCH_2, Bu, $ClCH_2CH_2$, Me, $MeOCH_2CH_2$, $PhCH_2$, Ph, p-ClC_6H_4

R_4 = Et, H, Bu, Me

NR_1R_2 = morpholino, 4-formylpiperazinyl

6-amino-4-oxo-5,4-dihydroisothiazolo [5,4-d] pyrimidines (V) show psychotropic and hypnotic sedative effects (9).

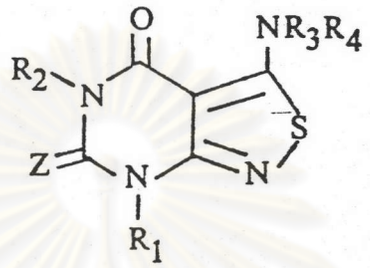


(V)

R = R_1 = Me

NR_2R_3 = morpholino

Isothiazolo [3,4-d] pyrimidines (VI) are useful as sedatives (10).



(VI)

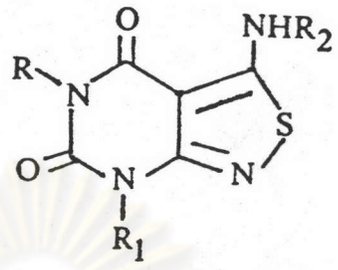
R_1, R_3 = alkyl, aryl

R_2, R_4 = alkyl

Z = O,S

4. Diuretic activity

3-Aminoisothiazolo [3,4-d] pyrimidines (VII) have been reported to exert diuretic activity (11).



(VII)

R = H, Me, Bu, Pr, CH_2Ph

R_1 = Me, Et, Pr, Bu, Ph, CH_2Ph, $(CH_2)_3OMe$, $(CH_2)_3OEt$, $(CH_2)3OCHMe_2$

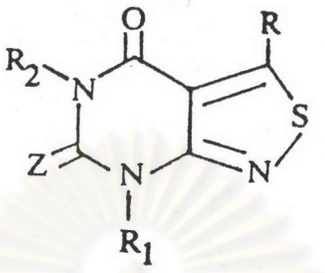
R_2 = H, $SO_2C_6H_4Me$-p

or R = R_1 = Me

R_2 = CO_2Et, COC_6H_4Cl-p, Bz, $SO_2C_6H_4Me$-p

5. Cyclic Nucleotide Phosphodiesterase Inhibiting activity

Isothiazolo [3,4-d] pyrimidine (VI) (10), (VIII) (14) have been reported to have adenosine-3,5-cyclicphosphatephosphodiesterase inhibiting activity.



(VIII)

R = NHR_3, NR_3R_4

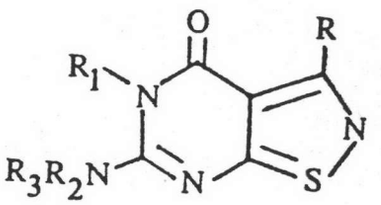
R_1 = R_2 = Et

R_3 = R_4 = Me

Z = O, S

6. Nucleoside Analog

Several aminoisothiazolopyrimidine derivatives such as 3-glycosylamino-5,7-dimethylisothiazolo [5,4-d] pyrimidine-4,6-diones (15,16) ; 5,7-dimethyl-3-[2,3,6-tri-O-acetyl-α -D-glucopyranosyl]-ß-D-glucopyranosyl]-ß-D-glucopyranosylaminoisothiazolo [3,4-d] pyrimidine-4,6-dione (17,18) were synthesized as the nucleoside analog.



(IX)

7. Antiinflammatory activity

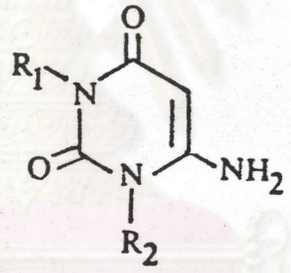
For many years, isothiazolo [3,4-d] pyrimidine derivatives have been synthesized and reported to have antiinflammatory activity. Such compounds include of (IV) (8), (VI) (10), (VII) (11).

Synthesis of Isothiazolo [3,4-d] pyrimidine Ring

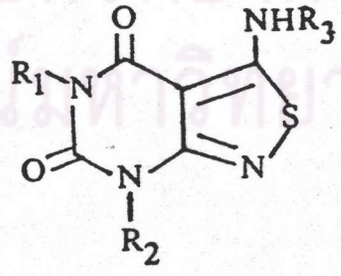
Many isothiazolo [3,4-d] pyrimidine derivatives have been synthesized in many laboratories for years. All of them were carried out via either aminouracil or isothiazole ring intermediate.

1. Azine approach

Roff Neiss *et al* (19) synthesized some isothiazolo [3,4-d] pyrimidine derivatives by the reaction of the aminouracil (X) with isothiocyanate (R_3NCS), then oxidative cyclization to give XI.



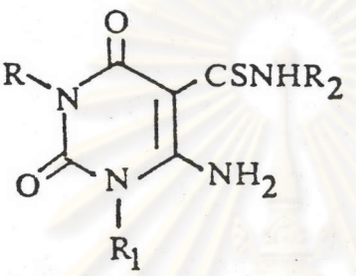
(X)



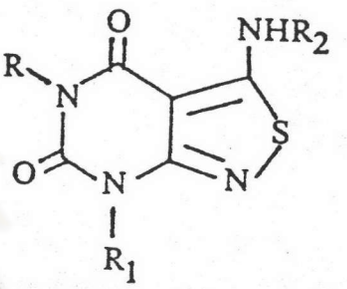
(XI)

R_1 = H, Pr ; R_2 = Me, Bu ; R_3 = H, $SO_2C_6H_4$-Me-4, COOEt

Later, they prepared some more isothiazolopyrimidine derivatives by cyclizing XII with sulfuric acid to give XIII which may be accompanied by hydrolysis of R_2 (11).



(XII)



(XIII)

R = H, Me, Bu, Pr, CH_2Ph

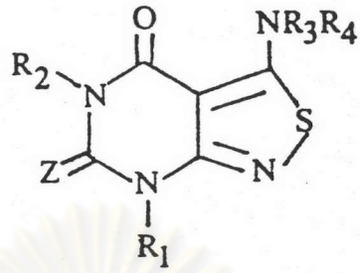
R_1 = Me, Et, Pr, Bu, Ph, CH_2Ph, $(CH_2)_3OMe$, $(CH_2)_3OEt$, $(CH_2)_3OCHMe_2$

R_2 = H, $SO_2C_6H_4Me$-p

R = R_1 = Me

R_2 = CO_2Et, COC_6H_4Cl-p, $SO_2C_6H_4Me$-p

Furukawa *et al* also used this procedure to prepared some derivatives of isothiazolo [3,4-d] pyrimidine XIV (10), XV (14).

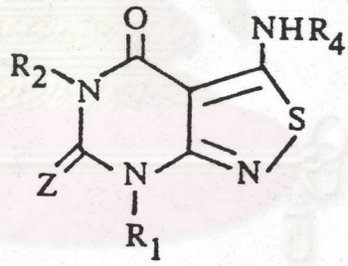


(XIV)

R_1, R_3 = alkyl, aryl

R_2, R_4 = alkyl

Z = O, S



(XV)

X = O, S

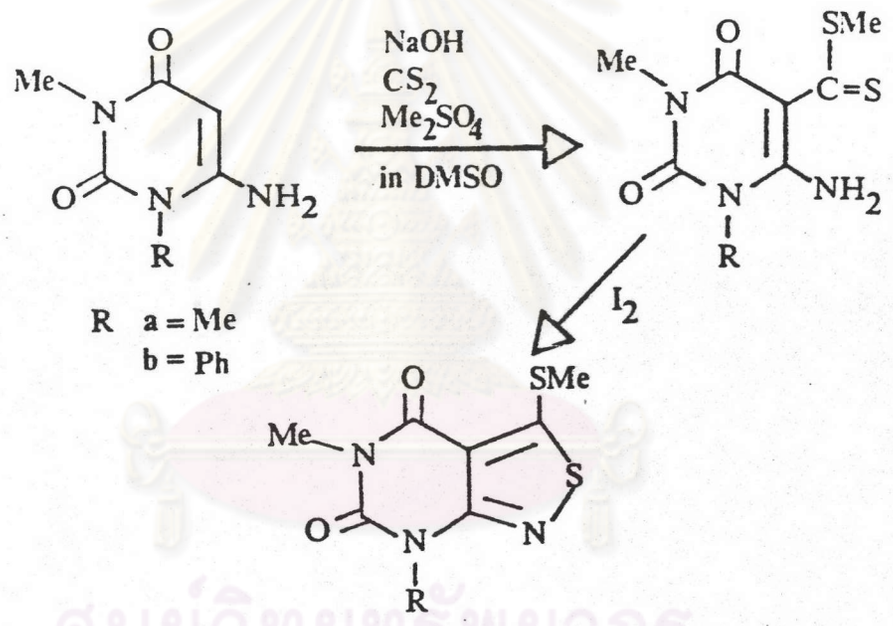
R_1 = H, alkyl, aryl, benzyl

R_2 = H, alkyl

R_3 = alkyl, aryl, benzyl

R_4 = alkyl

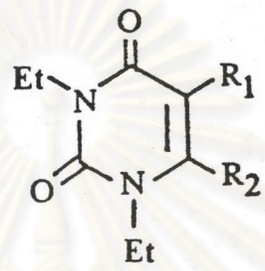
Okuda and coworkers (20) prepared 3-methyl-thioisothiazolo [3,4-d] pyrimidine-4,6-(5H,7H)-diones (XVI) by treatment of 6-aminouracil with carbon disulphide and dimethyl sulphate in the presence of alkali. The methyl-6-aminouracil-5-dithiocarboxylates obtained were reacted with iodine in dimethyl sulfoxide to give XVI in good yields.



(XVI)

Furukawa *et al* (21) synthesized the 3-amino-isothiazolo [3,4-d] pyrimidines in one-step by the reaction of 6-aminouracil and Vilsmeier reagents.

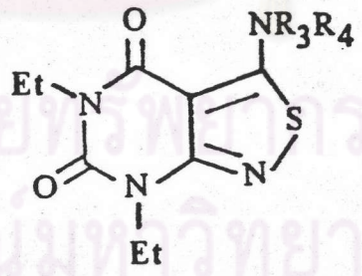
6-amino-1,3-diethyluracil (XVII) reacted with dimethylformamide-thionyl chloride to afford 5,7-diethyl-3-dimethylaminoisothiazolo [3,4-d] pyrimidine-4,6-(5H,7H)-dione (XVIII) and three minor products (XIX, XX, XXI).



XVII ; R_1 = H , R_2 = NH_2

XX ; R_1 = Cl , R_2 = N=CHNH_2

XXI ; R_1 = CHO, R_2 = N=CHNH_2

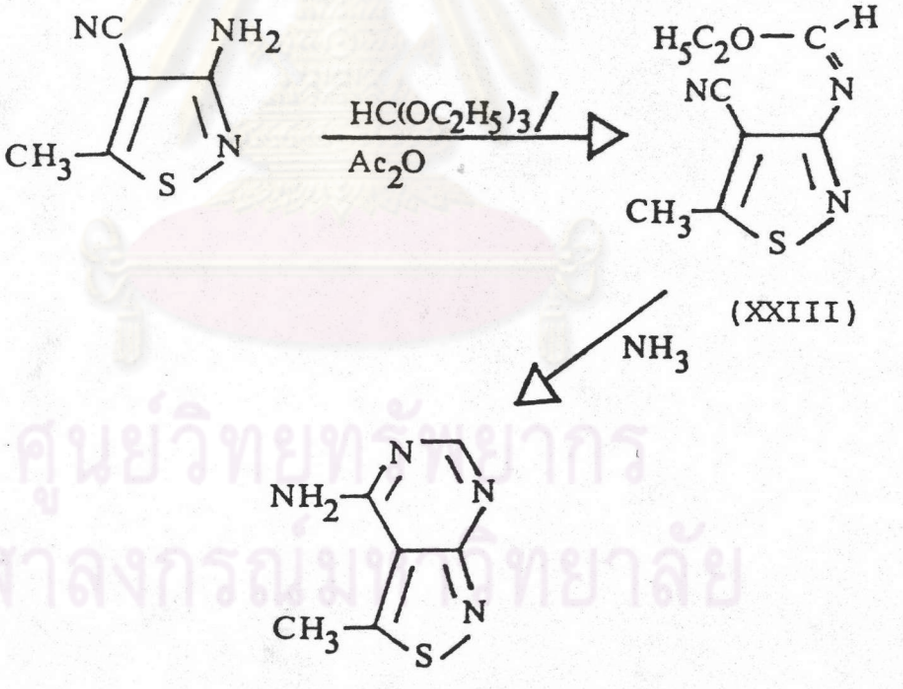


XVIII ; R_3 = R_4 = Me

XIX ; R_3 = H , R_4 = Me

2. Azole approach

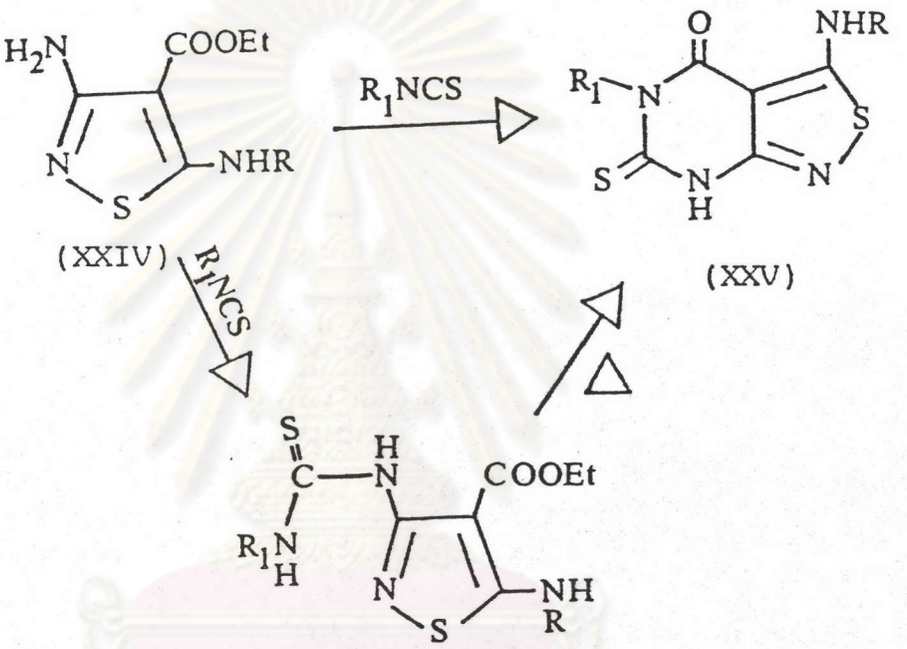
3-methyl-4-aminoisothiazolo [3,4-d] pyrimidine (XXII) is the first isothiazolo [3,4-d] pyrimidine reported by Hartku K. and Peohkar L.(22). It was carried out by the reaction of 3-amino-4-cyano-5-methylisothiazole with ethyl orthoformate and acetic anhydride to afford (XXIII) which with an excess of alcoholic ammonia yield (XXII).



(XXIII)

(XXII)

Recently, Akarapanichkorn S.(23) has synthesized many isothiazolo [3,4-d] pyrimidine derivatives (XXV) using 3,5-diaminoisothiazole (XXIV) to react with isothiocyanate derivatives.



a , R = R_1 = CH_3

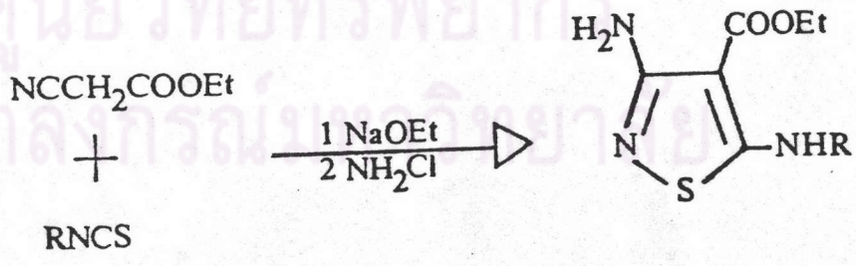
b , R = R_1 = Ph

c , R = CH_3 , R_1 = Ph

d , R = Ph , R_1 = CH_3

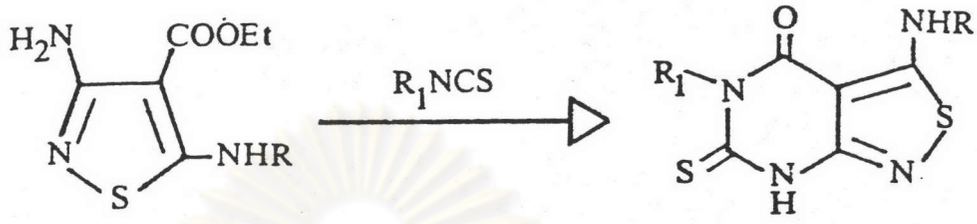
Of methods described above, the last method seems to correlate with our procedure in that the compounds obtained can be modified to yield target products. Since it has been known that in pyrimidine derivatives, the mercapto group is the most versatile for use in further transformation in its ability to undergo certain replacement reactions (24). It is synthetically comparable to a reactive halogen substitutent, but it also has certain advantages in this respect, for the mercapto compounds are more readily prepared, are more controllable in synthetic operations and more stable in storage. Therefore, the 5-substituted-3-(substituted) aminoisothiazolo [3,4-d] pyrimidine-4-one-6(7H)-thione (when methyl and phenyl are the substituting functional group) were first synthesized. These compounds can be performed in 2 steps.

1) Synthesis of 3,5-diaminoisothiazoles



R = CH_3, Ph

2) Synthesis of isothiazolo [3,4-d] pyrimidines



R = CH_3, Ph

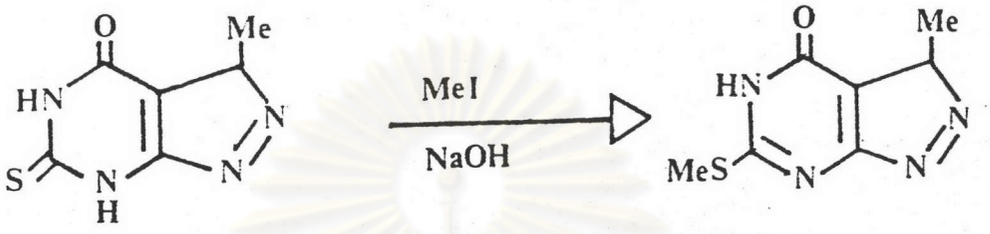
Derivatization of Isothiazolopyrimidine Derivatives

A. Synthesis of Methylsulphide of Isothiazolo pyrimidine Derivatives

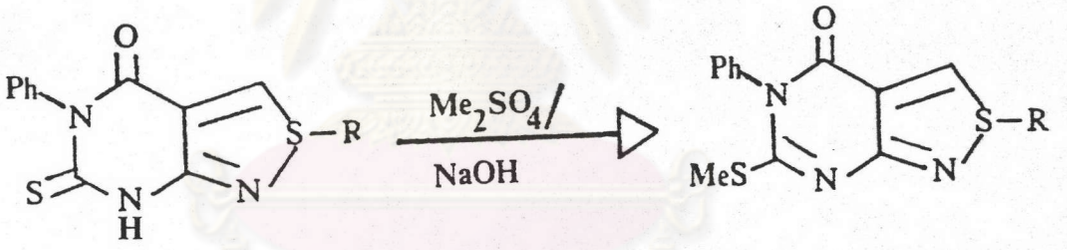
It has been known that the methylthio functional group on the heterocyclic rings, as well as some fused isothiazole derivatives, react with nucleophilic agent to give the corresponding substituted products (20). So, 5-substituted-6-methylthio-3-(substituted) aminoisothiazolo [3,4-d] pyrimidine-4-one, an intermediate for further transformation to the target compounds, were then synthesized.

Methylthioether compounds can be prepared by direct methylation to the thio functional group. It can

be accomplished by treating with methyl iodide, methyl hydrogen sulphate or dimethyl sulphate under alkali condition (25, 26, 27).



(XXVI) (XXVII)



(XXVIII) (XXIX)

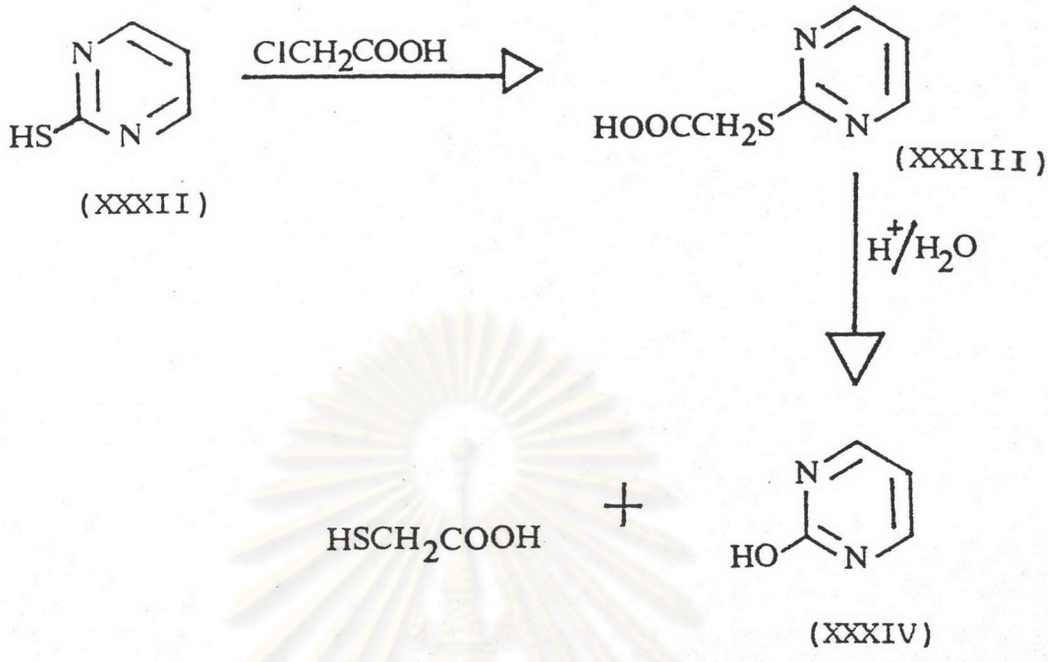
R = CH_3, $CH_2C_6H_5$

Since the alkyl sulphates often gives higher yield (25) and cheaper (28) than the alkyl halide, it is also the convenient reagent for S-methylation. Therefore, dimethyl sulphate in sodium hydroxide solution was chosen to methylate the thio group in the isothiazolopyrimidine derivatives.

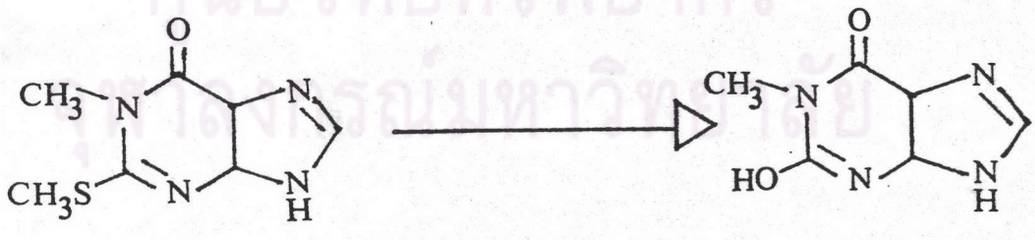
B. Replacement of Methylthio Substitutents by Hydroxyl Group

The reactive methyl sulphide of isothiazolo-pyrimidine derivatives obtained was acid hydrolysed to replace the methylthio group with hydroxyl group. The term hydrolysis is applied to reaction of both organic and inorganic chemistry wherein water effects a double decomposition with another compound, hydrogen going to a component, hydroxy to the other (25).

The mercapto ethers have been reported to be cleaved smoothly under acid condition and yield the oxygen analogs. This reaction has been elaborated into an elegant tool, involving formation of the carboxymethyl sulphide by reaction of the thiol (XXXII) with chloroacetic acid and subsequent acid clevage. The volatile thioglycollic acid is eliminated and excellent yield of the oxygen analog (XXXIV) obtained. The displacement depends on the nucleophilic attack on the positively charged carbon atom of the heterocyclic (24).



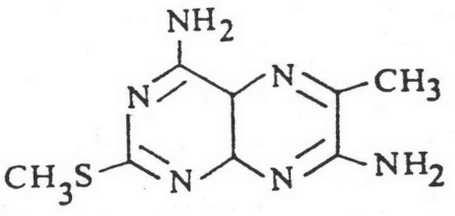
From the methylmercapto ether, many success in the acid hydrolysis reaction have been reported (29,30, 31, 32). For example, Elian (29) showed that 1-methyl xanthine (XXXVI) was prepared by acid hydrolysis of 1-methyl-2-methylthiopurine-6-one (XXXV) with 6 N hydrochloric acid under reflux conditions for 24 hours.



C. Replacement of Methylthio Substituents by Amines

The unaccountable difficulty in replacement of alkylthio groups in some pyrimidine derivatives has been noted on more than one occasion. Andrews *et al* (33) failed to convert the 5-nitro-4-amino-6-hydroxy-2-methylthiopyrimidine to the corresponding 2-amino by the reaction with ammonia under a variety of conditions. An exhaustive series of experiments was unsuccessful to directly replace the methylthio group in 2-methylthioadenine and 2-methylthio-9-methyladenine with an amino or substituted amino group. No reaction occured with saturated alcoholic ammonia below 230°C, and decomposition products to brown material when reaction was taken above 230 °C was obtained. No replacement could be effected when sodamide was used under various conditions, with aniline or with methylaniline and methylaniline hydrochloride at 170°C, or with ammonium chloride or acetamide at 160°C, a mixture of aniline and aniline hydrochloride at 170°C cause decomposition with formation of an unidentified substance (mp 255°C).

4,7-diamino-6-methyl-2-methylthiopteridine (XXXVII) failed to react with piperidine (34).



(XXXVII)

Elion *et al* (35) reported the first succession of the replacement of the 2-methylmercapto group of 6-hydroxy-2-methylmercaptopurine with some substituted amines. The reaction was carried out by heating 6-hydroxy-2-methylmercaptopurine with 3 or 4 molecule equivalent of amine in a seal tube at 140°C for 24 hours for alkylamine and 160°C for 48 hours for aromatic amine with or without solvents.

At present, there was no report concerning such replacement in the isothiazolopyrimidine derivatives.