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# A NEW SYNTHESIS OF 1,2,3-THIADIAZOLO[4,5-d]PYRIMIDINES

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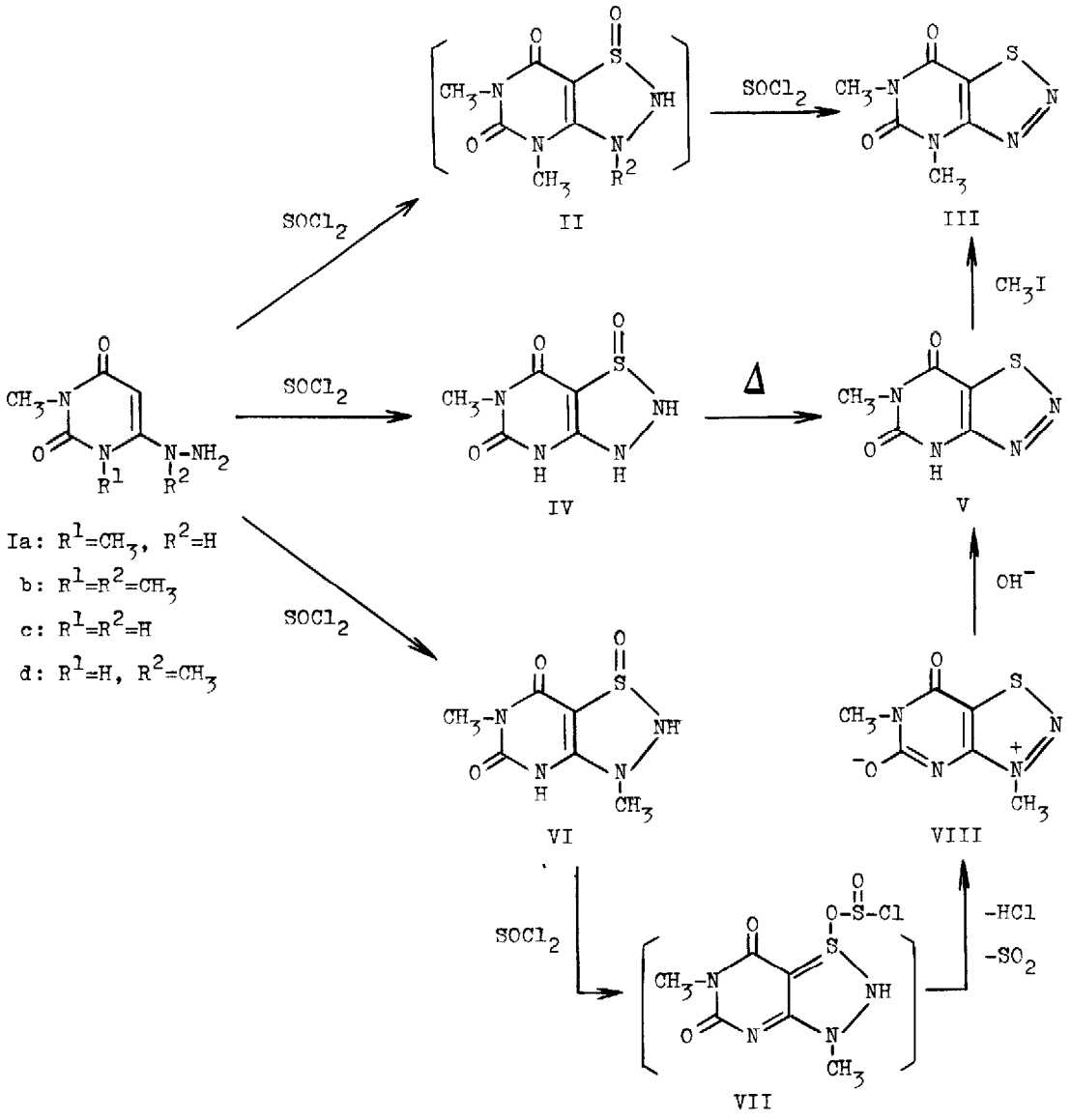
An isomer of thiadiazolopyrimidines, 1,2,3-thiadiazolo[4,5-d]pyrimidine, has not been previously reported. Our interest in developing potential nucleic acid enzyme inhibitors prompted us to synthesize a series of this new class of heterocycle combining the features of biologically important 5-mercaptopyrimidines with other fused pyrimidines such as pyrazolo[3,4-d]pyrimidines or v-triazolo[4,5-d]-pyrimidines.

Stirring of 1 part of 1,3-dimethyl-6-hydrazinouracil (Ia)[1] with 10 parts of thionyl chloride at 0° for 30 min afforded a good yield of 4,6-dimethyl-1,2,3-thiadiazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione (III), which was isolated by evaporation of the thionyl chloride in vacuo and addition of water. The structure of III was assigned on the basis of its spectral data [mass: m/e 198, uv $\lambda_{max}^{EtOH}$: 214nm (log ε 4.45), 242(sh, 3.81), 327(3.79), ir(nujol): 1715cm$^{-1}$(C=O), nmr(DMSO-$d_6$): δ 3.33(3H, s, $N^6$-$CH_3$), 3.83(3H, s, $N^4$-$CH_3$)] and elemental analysis. In particular, the uv spectrum of III[2] was quite similar with that of 6,8-dimethylpyridazino[3,4-d]pyrimidine-5,7(6H,8H)-dione[3]. It is interesting to note that the reaction of 1,3-dimethyl-6-(1'-methylhydrazino)uracil (Ib)[4] with thionyl chloride also gave III under the same condition. In these reactions, presumable intermediates, thiadiazoline-S-oxides (II), could not be isolated.

In contrast with the above results, treatment of 6-hydrazino-1-methyluracil (Ic)[5] with thionyl chloride at 0° for 30 min yielded the thiadiazoline-S-oxide(IV) [mass: m/e 202, ir(nujol): 1720(C=O), 1100cm$^{-1}$(S=O)], however, which was extremely unstable and underwent dehydration to afford 6-methyl-1,2,3-thiadiazolo[4,5-d]-pyrimidine-5,7(4H,6H)-dione (V) [mass: m/e 184, uv $\lambda_{max}^{EtOH}$: 212nm(log ε 4.23), 250


SOCl2
SOCl2
SOCl2
Δ
CH3I
OH⁻
SOCl2
-HCl
-SO2
II
III
IV
V
VI
VII
VIII
Ia: R1=CH3, R2=H
b: R1=R2=CH3
c: R1=R2=H
d: R1=H, R2=CH3

TABLE

Preparation of 1,2,3-Thiadiazolo[4,5-d]pyrimidine Derivatives

| Compound | Procedure | M.p. (°C)[a] (Recrystn. solvent) | Yield(%) |
|---|---|---|---|
| III | Ia + $SOCl_2$ (0°, 30min) | 140-141 (EtOH) | 83 |
| | Ib + $SOCl_2$ (0°, 30min) | | 78 |
| | V + $CH_3I$ + $K_2CO_3$ in DMF (160°, 2hr) | | 75 |
| IV | Ic + $SOCl_2$ (0°, 30min) | —[b] | 80 |
| V | IV in EtOH (90°, 5min) | 235 (dec.) (EtOH) | 100 |
| | VIII in 5% NaOH (90°, 1min) | | 49 |
| VI | Id + $SOCl_2$ (0°, 30min) | 182-185 (MeOH) | 87 |
| VIII | VI + $SOCl_2$ (90°, 15min) | 201-203 (EtOH) | 70 |
| | Id + $SOCl_2$ (90°, 15min) | | 61 |

a) All melting points were uncorrected. Satisfactory elemental analyses (C, H, N) were obtained for all products except IV.

b) Not determined.

(3.87), 320(3.83), ir(nujol): 1720cm$^{-1}$(C=O)] by the recrystallization from ethanol. The alkylation of V with methyl iodide led to III.

The reaction of 1-methyl-6-(1'-methylhydrazino)uracil (Id)[5] with thionyl chloride at 0° for 30 min provided the stable thiadiazoline-S-oxide (VI) [mass: m/e 216, uv $\lambda_{max}^{EtOH}$: 205nm(log ε 4.13), 265(4.25), 343(4.24), ir(nujol): 1715(C=O), 1115cm$^{-1}$(S=O)], which upon treatment with thionyl chloride at the elevated temperature resulted in the formation of a new class of mesoionic compound, anhydro-3,6-dimethyl-5-hydroxy-1,2,3-thiadiazolo[4,5-d]pyrimidinium-7(6H)-one hydroxide (VIII) [mass: m/e 198, uv $\lambda_{max}^{EtOH}$: 210nm(log ε 4.05), 242(4.22), 405(3.42), ir(nujol) : 1690cm$^{-1}$(C=O), nmr(DMSO-$d_6$): δ 3.23(3H, s, $N^6$-$CH_3$), 4.27(3H, s, $N^3$-$CH_3$)]. Compound VIII could also be obtained directly from Id by heating with thionyl chloride, however, an attempt to convert VI to VIII at 100° (dioxane) was shown to be ineffective. This fact suggested that the dehydration of VI to VIII proceeds *via* Pummerer reaction intermediate (VII). The mesoionic compound VIII was relatively stable in 10% HCl (150°, 30min), whereas the alkaline treatment of VIII (5% NaOH) immediately gave V.

The synthesis and properties of other 1,2,3-thiadiazolo[4,5-d]pyrimidines and their mesoionic derivatives are currently under investigation. The biological activity of the compounds described herein will be covered in a separate communication.

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