# Cyclization Reactions of 1,3-Dibromopropan-2-ol, 2,3-Dibromopropan-1-ol and 1-Bromomethyloxirane with 6-Amino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone



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The cyclization reactions, carried out in strongly- or weakly-basic media, are described. Sometimes, 7-amino-2,3-dihydro-3-hydroxymethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one is separated out, together with 8-amino-3,4-dihydro-3-hydroxy-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one, as the principal product. A mechanism of reaction, during which the cyclizating agents are changed into oxirane derivatives, is proposed. The results of single-crystal X-ray investigations on 8-amino-3,4-dihydro-3-hydroxy-7-nitroso-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one (R = 0.035 for 1013 reflections), and on 7-hydroxymethyl-6,7-dihydrothiazolo[3,2-*a*][1,2,3]triazolo[4,5-*d*]pyrimidin-9(1*H*)-one (R = 0.027 for 1607 reflections) are reported.

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In the course of the synthesis of 2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one and 3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one derivatives [1], the cyclization reaction of 6-amino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone (6-amino-2-thiouracil) (**1**) with 1,3-dibromopropan-2-ol (**2**) in strongly- or weakly-basic media was examined.

The method already employed for the condensation of **1** with 1,3-dibromopropane was used [1].

When **1** was reacted with **2** in the presence of more than two equivalents of 2*N* sodium hydroxide, a product (mp 230-232°) soluble in the reaction liquid was isolated, together with unknown compounds [2]. The spectral (uv, $^1$H-nmr, ir) characteristics of this compound and of its nitroso-, bromo- and amino-derivatives were not in accordance with those of 8-amino-3,4-dihydro-2*H*,6*H*-pyrimido-[2,1-*b*][1,3]thiazin-6-one derivatives, but with those of 7-amino-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one derivatives [1,3].

Table 1

| Reactants | medium | equivalents | yield % 4 | 9 | |
|---|---|---|---|---|---|
| 1 + 2 | 2*N* NaOH | 2.2 | 0 | 41 | [a] |
| | 1*N* NaOH | 2.0 | 34 | 25 | [a] |
| | 1*N* NaOH | 1.0 | 43 | 15 | [a] |
| | $Na_2CO_3$ | 4.0 | 87 | 8 | |
| 1 + 18 | 1*N* NaOH | 1.1 | 0 | 47 | [a] |
| | $Na_2CO_3$ | 4.0 | 49 | 17 | [a] |
| 1 + 19 | 2*N* NaOH | 1.0 | 0 | 54 | [a] |
| | 1*N* NaOH | 1.0 | 4 | 40 | [a] |
| | $Na_2CO_3$ | 4.0 | 28 | 38 | [a] |

[a] Together with unknown compounds.

When the reaction was carried out in less basic media (Table 1), a product (mp 260° dec) insoluble in the reaction liquid was isolated, together with the above-mentioned compound. The spectral (uv, $^1$H-nmr and ir) characteristics of this compound and of its nitroso-, bromo- and amino-derivatives were in good accordance with those of 8-amino-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*]-[1,3]thiazin-6-one derivatives [1].

In fact, the comparison of the uv, $^1$H-nmr and ir data (Table 2) of the two compounds, with mp 260° dec or 230-232°, and their nitroso-, bromo- or amino-derivatives, with those of parent compounds (*i.e.* 7-amino-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one and 8-amino-3,4-dihydro-2*H*-6H-pyrimido[2,1-*b*][1,3]thiazin-6-one) and their 5-nitroso-, 5-bromo- and 5-amino-derivatives [1], shows that the compound with mp 260° dec is an 8-amino-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one derivative, while the compound with mp 230-232° is a 7-amino-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one derivative.

In particular, the uv spectra of the compounds with the thiazine ring are characterized by two electronic bands in the 200-235 nm range [log $\epsilon$ (4.17-4.40)] and a broad band in the 280-340 nm range [log $\epsilon$ (3.60-3.90)]. The substitution of the thiazine with the thiazole ring affects the lower portion of the spectra ($\lambda < 235$ nm), where, except for the compound **7**, only one band is present.

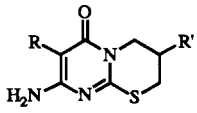
As previously observed [21], the introduction in both series of the compounds with substituents at 5-position induces a bathochromic effect on the band at higher $\lambda$ max. This effect is in accordance with the following order:

$$5\text{-H} < 5\text{-Br} < 5\text{-NH}_2 < 5\text{-NO}$$

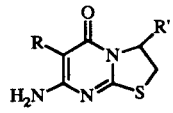
No effect was observed for the 3-OH and 3-$CH_2$OH substitution.

Table 2

$^1$H-NMR, UV and IR Spectral Data



3 7



8 12

| Compound | R | R' | $^1$H-NMR (δ ppm) [a] | UV λmax. (log ε) [b] | IR ($cm^{-1}$) [c] $NH_2$ | IR ($cm^{-1}$) [c] CO |
|---|---|---|---|---|---|---|
| **3** [1] | H | H | 6.37 (s, 2H, 8-$NH_2$), 4.86 (s, 1H, 7-H), 3.80 (t, 2H, 4-$CH_2$), 3.11 (t, 2H, 2-$CH_2$), 2.06 (m, 2H, 3-$CH_2$) | 281 (3.75), 234 (4.29), 218 (4.31) | 3400, 3165 | 1640, 1620 |
| **4** | H | OH | 6.35 (s, 2H, 8-$NH_2$), 5.53 (d, 1H, 3-OH), 4.86 (s, 1H, 7-H), 4.27 (m, 1H, 3-H), 4.00 (q, 1H, 4-CH), 3.53 (q, 1H, 4-CH), 3.28 (q, 1H, 2-CH), 2.99 (q, 1H, 2-CH) | 281 (3.80), 233 (4.34), 220 (4.39) | 3337, 3171 | 1655, 1619 |
| **5** [f] | NO | OH | 10.74 and 8.82 [d], 5.72 (s, 1H, 3-OH) [e], 4.46 (m, 1H, 3-H), 4.33 (q, 1H, 4-CH), 3.69 (q, 1H, 4-CH), 3.40 (q, 1H, 2-CH), 3.10 (q, 1H, 2-CH) | 343 (4.16), 270 (sh, 3.70), 218 (sh, 4.11), 203 (4.19) | 3323, 3192 | 1690, 1623 |
| **6** | Br | OH | 6.79 (broad, 2H, 8-$NH_2$), 5.57 (d, 1H, 3-OH), 4.32 (m, 1H, 3-H), 4.13 (q, 1H, 4-CH), 3.57 (d, 1H, 4-CH), 3.30 (q, 1H, 2-CH), 3.02 (q, 1H, 2-CH) | 292 (3.94), 234 (4.30), 219 (4.34) | 3468, 3153, 3270 | 1624 |
| **7** | $NH_2$ | OH | 5.66 (s, 2H, 8-$NH_2$), 5.21 (d, 1H, 3-OH), 4.25 (m, 1H, 3-H), 4.04 (q, 1H, 4-CH), 3.67 (broad, 2H, 7-$NH_2$), 3.53 (q, 1H, 4-CH), 3.24 (q, 1H, 2-CH), 2.96 (q, 1H, 2-CH) | 307 (3.86), 290 (sh, 3.85), 229 (4.21) | 3337, 3191 | 1665, 1624 |
| **8** [1] | H | H | 6.47 (s, 2H, 7-$NH_2$), 4.79 (s, 1H, 6-H), 4.17 (t, 2H, 3-$CH_2$), 3.41 (t, 2H, 2-$CH_2$) | 271 (3.62), 220 (4.30) | 3390, 3180 | 1630, 1600 |
| **9** | H | $CH_2OH$ | 6.49 (s, 2H, 7-$NH_2$), 5.20 (t, 1H, OH), 4.78 (s, 1H, 6-H), 4.74 (m, 1H, 3-H), 3.67-3.31 (envel, 4H, 03 and 2-$CH_2$) | 273 (3.84), 223 (4.50) | 3325, 3161 | 1654, 1619 |
| **10** | NO | $CH_2OH$ | 11.14 and 9.06 [d], 5.26 (t, 1H, 3-OH), 5.03 (m, 1H, 3-H), 3.86-3.74 (envel, 2H, CH), 3.64 (q, 1H, CH), 3.48 (q, 1H, CH) | 342 (4.17), 277 (sh, 3.68) 211 (4.19) | 3279, 3154 | 1644, 1619 |
| **11** | Br | $CH_2OH$ | 6.83 (s, 2H, 7-$NH_2$), 4.77 (m, 1H, 3-H), 4.35 (broad, 1H, OH), 3.71 (q, 1H, CH), 3.55 (envel, 2H, CH), 3.38 (q, 1H, CH) | 289 (3.86), 224 (4.42) | 3459, 3158 3292 | 1630 |
| **12** | $NH_2$ | $CH_2OH$ | 5.78 (s, 2H, 7-$NH_2$), 5.23 (broad, 1H, OH), 4.77 (m, 1H, 3-H), 4.20 (broad, 2H, 6-$NH_2$), 3.71-3.52 (envel, 3H, CH), 3.38 (d, 1H, CH) | 308 (sh, 3.85), 290 (3.87), 221 (4.29) | 3322, 3180 | 1659, 1620 |

[a] dimethyl sulfoxide-$d_6$. [b] In ethanol. [c] Frequency ranges (ν). [d] Two large singlets, attributable to intramolecular hydrogen bond NH--O=N. [e] In some samples the value shifted to a broad band falling around 5.8 ppm. [f] The ir values of another microcrystalline form are: 3394, 3286, 3130, 1679, 1623.

These structural assignments were confirmed by single-crystal X-ray analysis of two crystalline derivatives, **5** and **17**.

The structural attributions could be explained by means of the following sequences of reactions a) **1** + **2** → **13** → **4**, b) **1** + **2** → **13** → **14** → **4** and/or **9**, c) **1** + **2** → **1** + **18** → **14** → **4** and/or **9** (Scheme 1). In fact, **4** and **9** were also obtained by reacting **1** with 1-bromomethyloxirane (epibromidrine) (**18**) in different reaction media (Table 1) (Scheme 1).

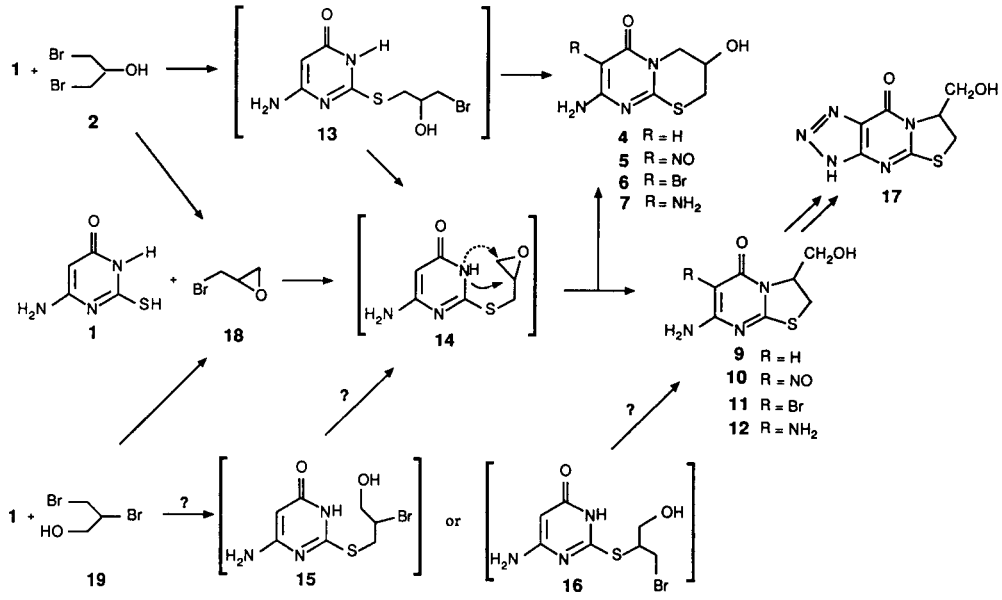
From the foregoing it is not clear, however, whether **2** changes into the oxirane ring before or after the reaction with **1**.

The literature would suggest that no cyclization reactions of **2** with 2-thiopyrimidine derivatives or with other similar 1,3-dinucleophilic structures are able to yield thiazole derivatives, that is, to cause 1,2-nucleophilic reaction [4-8]. Yet, it is known that **18** can undergo 1,2- [9,10] or 1,3-dinucleophilic substitution [11-12] and generate penta- or esatomic heterocyclic rings.

An answer to this question might be found in the reaction of **1** with 2,3-dibromopropan-1-ol (**19**).

Theoretically, **19** should react with **1** practically exclusively through the secondary halogenated carbon atom to give **16** and not **15**; **16** should give the isomeric derivative of **9**. If **19** is changed into epibromidrine (**18**) by strongly-basic media before reacting with **1**, the in-

SCHEME 1(*)




(*) Compounds in brackets have not been separated out.

Table 3
Crystallographic Data

| | Compound 5 | Compound 17 |
|---|---|---|
| Folrmula | $C_7H_8N_4O_3S$ | $C_7H_7N_5O_2S$ |
| Molecular Weight | 228.23 | 225.23 |
| Crystal System | orthorhombic | monoclinic |
| Space Group | Pbca ($D_{2h}^{15}$, No. 61) | $P2_1/c$ ($C_{2h}^5$, No. 14) |
| a, Å | 12.299 (2) | 9.478 (2) |
| b, Å | 8.467 (2) | 5.085 (1) |
| c, Å | 17.525 (2) | 18.317 (3) |
| β, deg | 90 | 93.27 (1) |
| V. Å$^3$ | 1825.0 (6) | 881.4 (7) |
| Z | 8 | 4 |
| $D_{calcd}$, g · cm$^{-3}$ | 1.661 | 1.697 |
| $D_{obsd}$, g · cm$^{-3}$ | 1.67 | 1.67 |
| F(000) | 944 | 464 |
| Radiation (λ, Å) | graphite monochromated Mo Kα (0.71069) | |
| Reflection measured | +h, +k, +1 | ±h, +k, +1 |
| Scan Type | ω - 2 θ | ω - 2 θ |
| θ Limits, deg | 2 - 26 | 2 - 28 |
| Scan Width, deg | 0.60 + 0.35 tan θ | 0.75 + 0.35 tan θ |
| Scan speed Limits, deg · min$^{-1}$ | 0.92 - 2.75 | 1.02 - 4.12 |
| Standard Reflections | 2 every 2 hours (no significant changes) | |
| No. of measured independent Reflections | 1777 | 2132 |
| No. of observed Reflections | 1013 with I>3 · σ (I) | 1607 with I>3 · σ (I) |
| Crystal Dimensions, mm | 0.33 x 0.20 x 0.14 | 0.42 x 0.35 x 0.22 |
| μ, cm$^{-1}$ | 2.9 | 3.0 |
| Transmission: max-min | 0.998 - 0.915 | 0.994 - 0.960 |
| No. of Varied Parameters | 136 | 162 |
| R | 0.035 | 0.027 |
| $R_w$ | 0.039 | 0.031 |
| w | $0.86/(\sigma^2(F)+0.0012F_O^2)$ | $1.0/(\sigma^2(F)+0.0004F_O^2)$ |
| Δρ; max-min, e · Å$^{-3}$ | +0.24 -0.19 | +0.22 -0.25 |

Unit cell parameters were derived from least-squares fit to the setting angles of 25 intense reflections in the 8-21° θ range.

termediate **14** and then the compounds **4** and **9** could be produced.

By reacting **1** with **19** in a solution of 2*N* sodium hydroxide, **9** was separated out in fairly good yield, while in a solution of sodium carbonate **9** was separated out in lower yield together with **4** (Table 1); the spectral and chemical characteristics of these last two compounds and of their nitroso-, bromo- and amino-derivatives are perfectly identical to those of **4** and **9**, obtained starting from **1** + **2** and **1** + **18**, respectively.

In conclusion, the fact that all three reactions yield the same compounds, **4** and **9**, leads one to suppose that the strategic intermediate is **14**, and that the formation of **4** and **9** in the first and third reaction can be explained by hypothesizing the formation of an oxirane ring. The stereochemical mechanism of the cyclization reactions of **14** to **4** and **9** was not examined.

Up to now, **13**, **14**, **15** and **16** have not been isolated and identified; studies on this subject are in progress.

Description of the Structures **5** and **17**.

Since both compounds contain one optically-active center [C(2)], the space group determination (centrosymmetric in either case) indicated that both compounds crystallize in racemic form.

In both compounds, the unit cell contains one crystallographically independent molecule.

In crystals of compound **5** the building units (Figure 1) are arranged in almost parallel layers, and each molecule is linked through hydrogen-bonding interactions to four other molecules from adjacent layers (Figure 3). As previously observed for other pyrimidine derivatives [13-15], the pyrimidinone ring of compound **5** shows small but significant distortions from planarity, in the pattern of atomic deviations ranging from 0.025 to -0.018 Å, and of torsion angles in the 5.1 - -4.2° interval. The extra-ring atoms N(3), N(4), O(2), and O(3) deviate from ring plane 0.020, -0.010, -0.006, and -0.041 Å, respectively. As shown by the short C-N bond distances of 1.320(5) and 1.345(5) Å, respectively, there is strong conjugation between the amino and nitroso groups and the ring.

Furthermore, the fundamental $sp^2$ character of these N atoms, resulting in a coplanar arrangement of their bonded atoms, determines the most suitable condition for a strong intramolecular hydrogen bonding interaction between $-NH_2$ and -NO groups.

The (O(2)...N(3) and O(2)...H separations are 2.618(4) and 1.94 Å, respectively, and the subtended angle 125°. Bond distances and angles within the thiazine ring are in the expected range [16] and the hydroxy group is bonded to the ring in axial position. The crystal packing is determined by two types of intermolecular hydrogen bonding interactions; the strongest one involves the -OH function and the -NO group with O...O and H...O distances of 2.742(4) and 1.87 Å, respectively, and O-H...O angle of 161°. A weaker contact occurs between the amino and carbonyl groups [N(3)...O(3) = 2.776(4) Å; H...O(3) = 2.46 Å; < N(3)-H...O(3) = 100°].

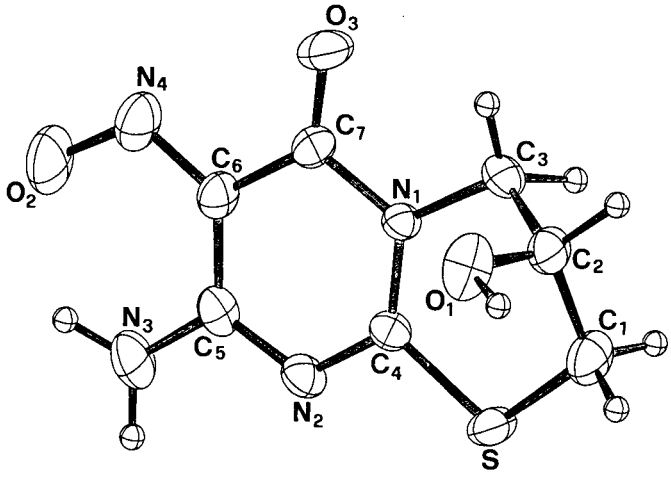



Figure 1. ORTEP [20] drawing showing atom-numbering scheme and thermal motion ellipsoids (50%) of compound **5**.

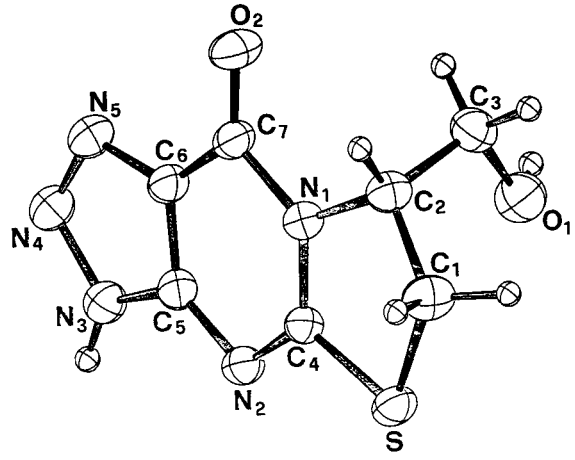



Figure 2. ORTEP drawing and atom-numbering scheme of compound **17**. Ellipsoids enclose 50% probability.

In crystals of compound **17** (Figures 2 and 4), the building units consist of centrosymmetrically related hydrogen-bonded pairs of molecules, linked through hydrogen bonds to neighbouring pairs. The distortions of the pyrimidinone ring plane are smaller than those of compound **5**; atomic deviations and torsion angles range from +0.009 to -0.014 Å, and from +2.1 to -2.3°, respectively. Comparison of pyrimidinone ring dimensions in **5** and **17** shows that the greatest differences involve the bond angles, namely, those at N(2), C(5), and C(7) atoms, and that smaller changes occur in bond distances. This could be interpreted as being due to geometrical constraints induced by two adjacent penta-atomic rings, rather than to the conjugative effects of the substituents. The thiazole

ring is planar within +0.002 Å, and makes a dihedral angle of 0.9° with the pyrimidinone ring plane. A relevant feature of the thiazole ring is a very narrow bond angle [92.4(1)°] at S atom.

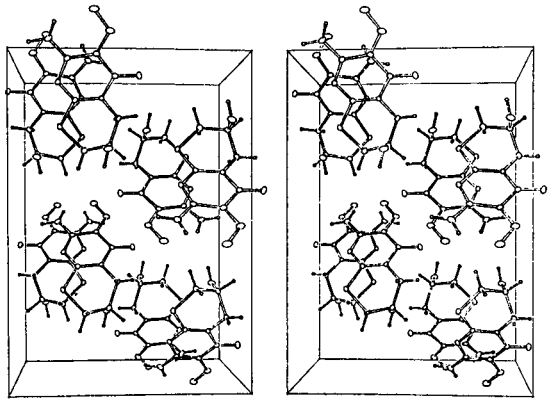


Figure 3. Stereoscopic view of the unit cell contents of compound **5** down the b axis with the a axis horizontal and c axis vertical.

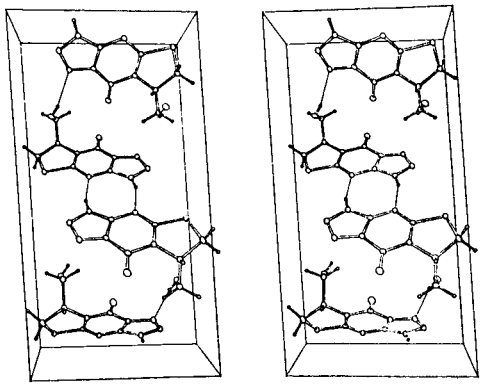


Figure 4. Stereoscopic view of the unit cell contents of compound **17** down the b axis with the a axis horizontal and c axis vertical. Still lines represent hydrogen bonds.

Like the -OH group of compound **5**, the $CH_2OH$ substituent is bonded to the cycle in axial position. The crystal packing is mainly determined by hydrogen bond interactions. Two centrosymmetrically related N-H...N hydrogen bonds link the molecules in dimeric units [N(3)...N(2) = 2.859(2)°; H...N(2) = 1.96(2) Å; <N(3)-H...N(2) = 164(2)°]. These dimeric units are linked to adjacent pairs by hydrogen bond interactions, which involve the -OH function and the triazole N(5) atom, with O...N and H...N distances of 2.933(2) and 2.20(3) Å, respectively, and a subtended angle of 171(3)°.

## EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. The ir spectra were recorded in Nujol suspen-

Table 4

Final Fractional Coordinates and Equivalent Isotropic Thermal Parameters for Compound 5

$$B_{eq} = 1/3\Sigma_i \Sigma_j B_{ij} \alpha_i^* \alpha_j^* a_i \cdot a_j$$

| Atom | x | y | z | $B_{eq}$, Å$^2$ |
|---|---|---|---|---|
| S | 0.20595(7) | 0.6218(1) | 0.28323(5) | 2.72(3) |
| C(1) | 0.3084(3) | 0.6754(5) | 0.2140(2) | 3.4(2) |
| C(2) | 0.4145(3) | 0.5883(4) | 0.2247(2) | 2.7(1) |
| O(1) | 0.4076(2) | 0.4279(3) | 0.2064(1) | 3.7(1) |
| C(3) | 0.4518(3) | 0.6007(4) | 0.3067(2) | 2.9(1) |
| N(1) | 0.3817(2) | 0.5054(3) | 0.3573(1) | 1.91(9) |
| C(4) | 0.2718(2) | 0.5105(4) | 0.3519(2) | 2.0(1) |
| N(2) | 0.2043(2) | 0.4380(3) | 0.3973(2) | 2.5(1) |
| C(5) | 0.2452(3) | 0.3454(4) | 0.4529(2) | 2.4(1) |
| N(3) | 0.1745(3) | 0.2730(4) | 0.4976(2) | 3.4(1) |
| C(6) | 0.3600(3) | 0.3240(4) | 0.4627(2) | 2.4(1) |
| N(4) | 0.4113(3) | 0.2341(4) | 0.5147(2) | 3.6(1) |
| O(2) | 0.3503(3) | 0.1582(4) | 0.5610(2) | 4.6(1) |
| C(7) | 0.4331(3) | 0.4068(4) | 0.4116(2) | 2.4(1) |
| O(3) | 0.5319(2) | 0.3994(3) | 0.4122(2) | 3.8(1) |
| H(C1a) | 0.3185 | 0.7932 | 0.2219 | 4.1 |
| H(C1b) | 0.2824 | 0.6599 | 0.1588 | 4.1 |
| H(C2) | 0.4775 | 0.6452 | 0.1901 | 3.6 |
| H(O1) | 0.3918 | 0.4231 | 0.1561 | 4.6 |
| H(C3a) | 0.5244 | 0.5559 | 0.3100 | 3.6 |
| H(C3b) | 0.4430 | 0.7359 | 0.3146 | 3.6 |
| H(N3a) | 0.1996 | 0.1928 | 0.5322 | 4.2 |
| H(N3b) | 0.0997 | 0.2826 | 0.4893 | 4.2 |

Table 5

Final Fractional Coordinates and Equivalent Isotropic Thermal Parameters for Compound 17

$$B_{eq} = 1/3\Sigma_i \Sigma_j B_{ij} \alpha_i^* \alpha_j^* a_i \cdot a_j$$

| Atom | x | y | z | $B_{eq}$, Å$^2$ |
|---|---|---|---|---|
| S | 0.89493(4) | 0.29837(8) | 0.92907(2) | 2.56(1) |
| C(1) | 0.9416(2) | 0.5800(4) | 0.8749(1) | 2.85(6) |
| C(2) | 0.8105(2) | 0.6582(3) | 0.82704(8) | 2.42(5) |
| C(3) | 0.8101(2) | 0.5483(3) | 0.75020(9) | 2.86(6) |
| O(1) | 0.8284(1) | 0.2723(3) | 0.75318(7) | 3.43(5) |
| N(1) | 0.6874(1) | 0.5573(2) | 0.86450(6) | 2.19(4) |
| C(4) | 0.7156(2) | 0.3553(3) | 0.91274(7) | 2.09(5) |
| N(2) | 0.6218(1) | 0.2184(3) | 0.94606(7) | 2.37(4) |
| C(5) | 0.4872(2) | 0.2990(3) | 0.92686(8) | 2.27(5) |
| N(3) | 0.3655(1) | 0.2017(3) | 0.95005(7) | 2.62(5) |
| N(4) | 0.2540(1) | 0.3393(3) | 0.91954(8) | 2.94(5) |
| N(5) | 0.3030(1) | 0.5219(3) | 0.87801(7) | 2.80(5) |
| C(6) | 0.4468(2) | 0.5026(3) | 0.88094(8) | 2.37(5) |
| C(7) | 0.5497(2) | 0.6540(3) | 0.84461(8) | 2.41(5) |
| O(2) | 0.5324(1) | 0.8386(2) | 0.80330(7) | 3.23(4) |
| H(C1a) | 0.973(2) | 0.721(4) | 0.907(1) | 3.7(3) |
| H(C1b) | 1.022(2) | 0.535(4) | 0.845(1) | 3.7(3) |
| H(C2) | 0.804(2) | 0.851(4) | 0.824(1) | 3.3(4) |
| H(C3a) | 0.894(2) | 0.633(4) | 0.725(1) | 3.3(3) |
| H(C3b) | 0.721(2) | 0.600(4) | 0.724(1) | 3.3(3) |
| H(O1) | 0.788(3) | 0.214(5) | 0.722(2) | 6.3(8) |
| H(N3) | 0,352(2) | 0.063(4) | 0.982(1) | 4.0(4) |

Table 6

Bond Distances (Å) and Bond Angles (deg) for Compound **5**

| | | | |
|---|---|---|---|
| S-C(1) | 1.808(4) | C(1)-C(2) | 1.511(5) |
| C(2)-O(1) | 1.397(4) | C(2)-C(3) | 1.512(5) |
| C(3)-N(1) | 1.477(4) | N(1)-C(4) | 1.355(4) |
| C(4)-S | 1.730(3) | C(4)-N(2) | 1.304(4) |
| N(2)-C(5) | 1.348(5) | C(5)-N(3) | 1.320(5) |
| C(5)-C(6) | 1.434(5) | C(6)-N(4) | 1.345(5) |
| N(4)-O(2) | 1.279(4) | C(6)-C(7) | 1.449(5) |
| C(7)-N(1) | 1.415(4) | C(7)-O(3) | 1.217(4) |
| C(4)-S-C(1) | 106.1(2) | S-C(1)-C(2) | 113.3(3) |
| C(1)-C(2)-O(1) | 113.3(3) | C(3)-C(2)-O(1) | 107.7(3) |
| C(1)-C(2)-C(3) | 110.3(3) | C(2)-C(3)-N(1) | 110.8(3) |
| C(3)-N(1)-C(4) | 121.5(3) | C(3)-N(1)-C(7) | 117.7(3) |
| C(7)-N(1)-C(4) | 120.8(3) | N(1)-C(4)-S | 122.2(2) |
| N(1)-C(4)-N(2) | 125.3(3) | S-C(4)-N(2) | 112.5(2) |
| C(4)-N(2)-C(5) | 118.5(3) | N(2)-C(5)-C(6) | 121.8(3) |
| N(2)-C(5)-N(3) | 116.9(3) | C(6)-C(5)-N(3) | 121.2(3) |
| C(5)-C(6)-C(7) | 118.5(3) | C(5)-C(6)-N(4) | 127.9(3) |
| N(4)-C(6)-C(7) | 113.6(3) | C(6)-N(4)-O(2) | 116.0(3) |
| C(6)-C(7)-N(1) | 115.0(3) | C(6)-C(7)-O(3) | 126.1(3) |
| N(1)-C(7)-O(3) | 118.8(3) | | |

Table 7

Bond Distances (Å) and Bond Angles (deg) for Compound **17**

| | | | |
|---|---|---|---|
| S-C(1) | 1.811(2) | C(1)-C(2) | 1.532(2) |
| C(2)-C(3) | 1.514(2) | C(3)-O(1) | 1.415(2) |
| C(2)-N(1) | 1.479(2) | N(1)-C(4) | 1.371(2) |
| C(4)-S | 1.733(1) | C(4)-N(2) | 1.308(2) |
| N(2)-C(5) | 1.366(2) | C(5)-C(6) | 1.374(2) |
| C(5)-N(3) | 1.347(2) | N(3)-N(4) | 1.361(2) |
| N(4)-N(5) | 1.303(2) | N(5)-C(6) | 1.365(2) |
| C(6)-C(7) | 1.436(2) | C(7)-N(1) | 1.422(2) |
| C(7)-O(2) | 1.211(2) | | |
| C(4)-S-C(1) | 92.4(1) | S-C(1)-C(2) | 107.7(1) |
| C(1)-C(2)-C(3) | 113.3(1) | C(1)-C(2)-N(1) | 106.3(1) |
| N(1)-C(2)-C(3) | 110.1(1) | C(2)-C(3)-O(1) | 109.6(1) |
| C(2)-N(1)-C(4) | 115.4(1) | C(2)-N(1)-C(7) | 119.8(1) |
| C(7)-N(1)-C(4) | 124.5(1) | N(1)-C(4)-S | 112.9(1) |
| N(1)-C(4)-N(2) | 125.9(1) | S-C(4)-N(2) | 121.1(1) |
| C(4)-N(2)-C(5) | 111.7(1) | N(2)-C(5)-C(6) | 127.4(1) |
| N(2)-C(5)-N(3) | 127.8(1) | C(6)-C(5)-N(3) | 104.8(1) |
| C(5)-N(3)-N(4) | 109.9(1) | N(3)-N(4)-N(5) | 108.2(1) |
| N(4)-N(5)-C(6) | 108.3(1) | N(5)-C(6)-C(5) | 108.7(1) |
| N(5)-C(6)-C(7) | 130.3(1) | C(5)-C(6)-C(7) | 121.0(1) |
| C(6)-C(7)-N(1) | 109.5(1) | C(6)-C(7)-O(2) | 129.3(1) |
| N(1)-C(7)-O(2) | 121.2(1) | | |

sion on a Perkin Elmer Spectrophotometer Mod 681. The uv spectra were obtained with a Perkin Elmer Spectrophotometer Model Lambda 15, using 1 cm quartz cells in $10^{-5}$ *M* ethanolic solution. The absorption maxima are reported in nanometers. The $^1$H-nmr spectra were recorded by Dr. A. Benedetti with a Varian Spectrometer Model XL 200 (Centro Interdipartimentale Grandi Strumenti, Modena University) in DMSO-$d_6$ solution. Chemical shifts are reported in ppm from tetramethylsilane, used as internal standard, and are given in $\delta$ units. The following abbreviations used to designate the multiplicity of individual signals: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Professor I. Moretti of Dipartimento di Chimica, Modena University, was of great assistance in interpreting the $^1$H-nmr spectra. Microanalyses were carried out by Miss S. Selmi in the Microanalysis Laboratory of the Dipartimento di Scienze Farmaceutiche, Modena University. We are grateful to these colleegues for their cooperation.

Crystallography.

Crystals of **5** and **17** were grown by slow cooling and then evaporation at room temperature of an aqueous solution of the compounds.

The crystals selected for X-ray analysis were sealed to a glass fiber and transferred directly to a CAD4 Enraf-Nonius single-crystal diffractometer. All measurements were carried out at room temperature, under the conditions listed in Table 3. The intensities were corrected for Lorentz and polarization effects, and an empirical absorption correction, based on the $\psi$ scan, was applied. The space groups were determined uniquely from a survey of systematic absences.

Both structures were resolved by direct methods by means of the SHELX-86 program [17], and were refined through full-matrix least-squares calculations with $\Sigma w(|Fo|-|Fc|)^2$ being minimized [18]. In both cases, all non-hydrogen atoms were treated anisotropically. The hydrogen atoms were located by means of $\Delta F$ Fourier maps, and were refined isotropically (with common temperature factors for hydrogens bonded to the same carbon atom) only for the compound **17**. Owing to the low reflection/parameter ratio, the hydrogen atoms of compound **5** were treated as fixed contributors at their observed positions, with assigned temperature factors 1.0 Å$^2$ higher than the bonded atoms. Least-squares refinement of these models led to final conventional R factors of 0.035 and 0.027 for compound **5** and **17**, respectively. The highest residual on the final, featureless $\Delta F$ Fourier maps are reported in Table 3. No trends of $\Sigma w\Delta^2$ as a function of $\sin\theta$, Fo, or Miller indices were observed. There was no evidence of secondary extinction.

Complex neutral-atom scattering factors, including anomalous dispersion terms for all non-hydrogen atoms were taken from International Tables for X-ray Crystallography [19]. Major calculations were carried out on a VAX 6310 computer.

Final coordinates and equivalent isotropic temperature factors are given in Table 4 and 5. Bond distances involving non-hydrogen atoms are reported in Tables 6 and 7. Lists of anisotropic thermal parameters, interatomic distances and angles involving hydrogen atoms, selected least-squares planes, torsion angles and observed and calculated structure factors are available on request from the author**.

8-Amino-3,4-dihydro-3-hydroxy-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one (**4**) and 7-Amino-2,3-dihydro-3-hydroxymethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**9**).

Propan-2-ol (40 ml) was added to an equal volume of a 2*N* or 1*N* sodium hydroxide or to a sodium carbonate solution (7.5 g, 70 mmoles, in 70 ml of water) containing 6-amino-2-thiouracil (**1**) (5 g, 35 mmoles); 1,3-dibromopropan-2-ol (**2**) (4.0 ml, 38 mmoles) was then stirred in dropwise at room temperature, stirring continuing at the same temperature for 1 hour and then at 60° for another 6 hours. After being left to stand overnight at room temperature, the insoluble fraction was collected and treated with a solution of sodium carbonate. The insoluble residue was found to consist of **4**, mp 260° dec (water).

*Anal.* Calcd. for $C_7H_9N_3O_2S$: C, 42.20; H, 4.55; N, 21.09. Found: C, 42.18; H, 4.58; N, 21.15.

The filtrate, saturated with carbon dioxide, was dried out under vacuum; the resultant residue was washed with ethyl ether and treated with a solution of sodium carbonate; the insoluble residue consisted of **9**, mp 230-232° (water).

*Anal.* Calcd. for $C_7H_9N_3O_2S$: C, 42.20; H, 4.55; N, 21.09. Found: C, 41.96; H, 4.62; N, 20.88.

The reaction between **1** and 1-bromomethyloxirane (**18**) or 2,3-dibromopropan-1-ol (**19**) was carried out under the same conditions and with the molecular quantities used in the preceding reactions.

The structures of the compounds obtained in these last two reactions were confirmed as **4** and **9**, respectively, by means of ir, $^1$H-nmr and uv spectra, mixed melting points and elementary analysis.

8-Amino-3,4-dihydro-3-hydroxy-7-nitroso-2*H*,6*H*-pyrimido[2,1-*b*]-[1,3]thiazin-6-one (**5**) and 7-Amino-2,3-dihydro-3-hydroxymethyl-6-nitroso-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**10**).

Compound **4** or **9** (2 g, 10 mmoles), finely powdered, was added slowly into a stirred solution of 15% acetic acid (40 ml) at 40-45° to increase solubility. The suspension was cooled to room temperature, sodium nitrite (0.76 g, 11 mmoles) was slowly added and stirring continued at the same temperature for another 6 hours. The blue product formed was collected and crystallized to give **5**, yield 90%, mp 225° dec (water).

*Anal.* Calcd. for $C_7H_8N_4O_3S$: C, 36.84; H, 3.53; N, 24.55. Found: C, 36.67; H, 3.41; N, 24.54.

Compound **10** was obtained in 88% yield, mp 300° (DMF-ethyl ether).

*Anal.* Calcd. for $C_7H_8N_4O_3S$: C, 36.84; H, 3.53; N, 24.55. Found: C, 37.10; H, 3.71; N, 24.24.

The ir spectral data show that **5** exists in two different crystalline forms (Table 2). For X-ray analysis, the prismatic violet crystalline form was used; the other, present in microcrystalline form, was unsuitable for diffractometric measurements.

8-Amino-7-bromo-3,4-dihydro-3-hydroxy-2*H*,6*H*-pyrimido[2,1-*b*]-[1,3]thiazin-6-one (**6**) and 7-Amino-6-bromo-2,3-dihydro-3-hydroxymethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**11**).

Bromine (0.47 g, 6 mmoles) was stirred dropwise into a solution of **4** or **9** (1 g, 5 mmoles) in glacial acetic acid (30 ml). The reaction mixture was stirred at room temperature for 8 hours and left to stand overnight. The resultant precipitate was collected, washed with ethyl ether and treated with a solution of sodium carbonate until alkaline *p*H. Compound **6** was obtained in 86% yield, mp 240-242° dec (methanol/ethyl ether).

*Anal.* Calcd. for $C_7H_7BrN_3O_2S$: C, 30.22; H, 2.89; N, 15.10. Found: C, 29.98; H, 2.70; N, 14.92.

Compound **11** was obtained in 60% yield, mp 230° dec (DMF/ethyl ether).

*Anal.* Calcd. for $C_7H_7BrN_3O_2S$: C, 30.22; H, 2.89; N, 15.10. Found: C, 29.94; H, 2.91; N, 14.80.

7,8-Diamino-3,4-dihydro-3-hydroxy-2*H*,6*H*-pyrimido[2,1-*b*][1,-3]thiazin-6-one (**7**) and 6,7-Diamino-2,3-dihydro-3-hydroxymethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**12**).

Method A.

Recently-purchased sodium hydrosulfide was added slowly to a suspension of nitroso derivative **5** or **10** (1 g) in boiling water (15 ml) until the blue colour completely disappeared. The solution was refluxed for 5 minutes and then refrigerated for 2 hours. The resultant precipitate, washed with water, consisted of **7** or **12**, respectively.

Compound **7** was obtained in 55% yield, mp 236-239° (DMF/ethyl ether).

*Anal.* Calcd. for $C_7H_{10}N_4O_2S$: C, 39.23; H, 4.70; N, 26.15. Found: C, 39.17; H, 4.70; N, 25.85.

Compound **12** was obtained in 63% yield, mp 252-254° (DMF/ethyl ether).

*Anal.* Calcd. for $C_7H_{10}N_4O_2S$: C, 39.23; H, 4.70; N, 26.15. Found: C, 39.21; H, 4.58; N, 25.89.

Method B.

Compounds **7** and **12** were also prepared by stirring **5** and **10** (0.5 g), suspended in methanol (25 ml) with hydrogen/Pd (1.5 atmospheres) for 8-12 hours. After evaporation of the solvent, the insoluble residue was extracted with a little DMF and crystallized by DMF/ethyl ether. The yield of **7** was 48%; that for **12** was 65%.

6,7-Dihydro-7-hydroxymethylthiazolo[3,2-*a*][1,2,3]triazolo[4,5-*d*]-pyrimidin-9(1*H*)-one (**17**).

Crystalline sodium nitrite (0.22 g, 32 mmoles) was added slowly into a stirred solution of **12** (0.7 g, 32 mmoles) in 20 ml of hydrochloric acid (1:1 v:v) in an ice bath at 0°. The solution was stirred for 7 hours and left to stand overnight at room temperature. Subsequent evaporation under vacuum yielded **17**, yield 55%, mp 215° dec (water); ir: $\nu$ max cm$^{-1}$ 3389, 3030, 1782, 1732; uv (ethanol): $\lambda$ max nm (log $\epsilon$) 267 (4.11), 229 (4.08), 205 (4.14).

*Anal.* Calcd. for $C_7H_7N_5O_2S$: C, 37.33; H, 3.13; N, 31.10. Found: C, 37.22; H, 3.10; N, 31.19.

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