Synthetic Routes to Thiazolo[3,2-*a*]pyrimidin-7-ones *via* 1-Allyl-2-thiouracil

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The reaction of 1-allyl-2-thiouracil (**4**) with I_2–AgOAc in refluxing AcOH proceeds to 2-methyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**5**) *via* a series of intramolecular transformations. The intermediates, 2-iodomethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one hydroiodide (**6**) and 2,3-dihydro-2-methylene-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**10**), were investigated. The syntheses are also described of 1-allyl-5-bromo-2-thiouracil (**9**), 2-acetoxymethyl- (**11**) and the hydrobromide of 2-bromomethyl- (**14**) 7*H*-thiazolo[3,2-*a*]pyrimidin-7-ones.

As reported previously, 2,3-dihydro-2-hydroxymethyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (**3**; R = H)[1] and its 6-methyl analogue (**3**; R = Me)[2] were obtained by intramolecular cyclisation reactions of the suitably activated 1-(2,3-dihydroxypropyl)uracil (**2**; R = H)[3] and 1-(2,3-dihydroxypropyl)thymine (**2**; R = Me),[4] respectively. The dihydroxy compounds (**2**; R = H and Me) were successfully prepared from 1-allyluracil (**1**; X = O, R = H) and 1-allylthymine (**1**; X = O, R = Me) by I_2–AgOAc oxidation.[5] These results prompted us to check whether 1-allyl-2-thiouracil (**4**) can undergo such a hydroxylation. The prop-2′-enyl structure (**4**) was formed from silylated 2-thiouracil and allyl bromide in acetonitrile[6] and clearly evidenced by ^{1}H n.m.r. signals for the allylic 2′c, 3′a, and 3′b protons. However, when (**4**) was allowed to react with I_2–AgOAc in refluxing AcOH, 2-methyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**5**) was isolated in 73% yield, as a product of a series of intramolecular displacements and rearrangements. The ^{1}H n.m.r. spectrum of (**5**) revealed a singlet with secondary splitting at δ 2.34 (*J* 1.2 Hz) for the 2-methyl group and a downfield resonance at δ 6.96 (*J* 1.2 Hz) for the C-3 aromatic proton. It is noteworthy that thiazolo[3,2-*a*]pyrimidin-7-one was previously obtained as a 5,6-dihydro-3-methyl derivative[7] from 2-aminothiazole and methyl acrylate in the presence of hydroquinone.

The conversion of (**4**) into (**5**) by the I_2–AgOAc procedure[5] was certainly initiated by the formation of the 2′,3′-iodonium ion (**4a**) which, in a thermodynamically governed reaction, underwent an internal nucleophilic attack of the C-2 sulphur atom[8] at the C-2′ position rather than at the C-3′ position to give an intermediate of type (**4b**). An experiment was therefore performed with I_2–CH_2Cl_2 only, and 2-iodomethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one resulted as a hydroiodide (**6**). For comparative experiments, the bromination of (**4**) afforded the analogous 2-bromomethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one hydrobromide (**7**), almost in quantitative yield. Spontaneous crystallizations of the bicyclic products (**6**) and (**7**), as stable hydrohalides, facilitated their separations. Unstable and oily 2-bromomethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**8**) was isolated from (**7**) on treatment with an equimolar amount of Na_2CO_3. The ^{1}H n.m.r. spectra of (**6**) and (**7**) were consistent with those of the analogous bicyclic hydroxy compounds (**3**).

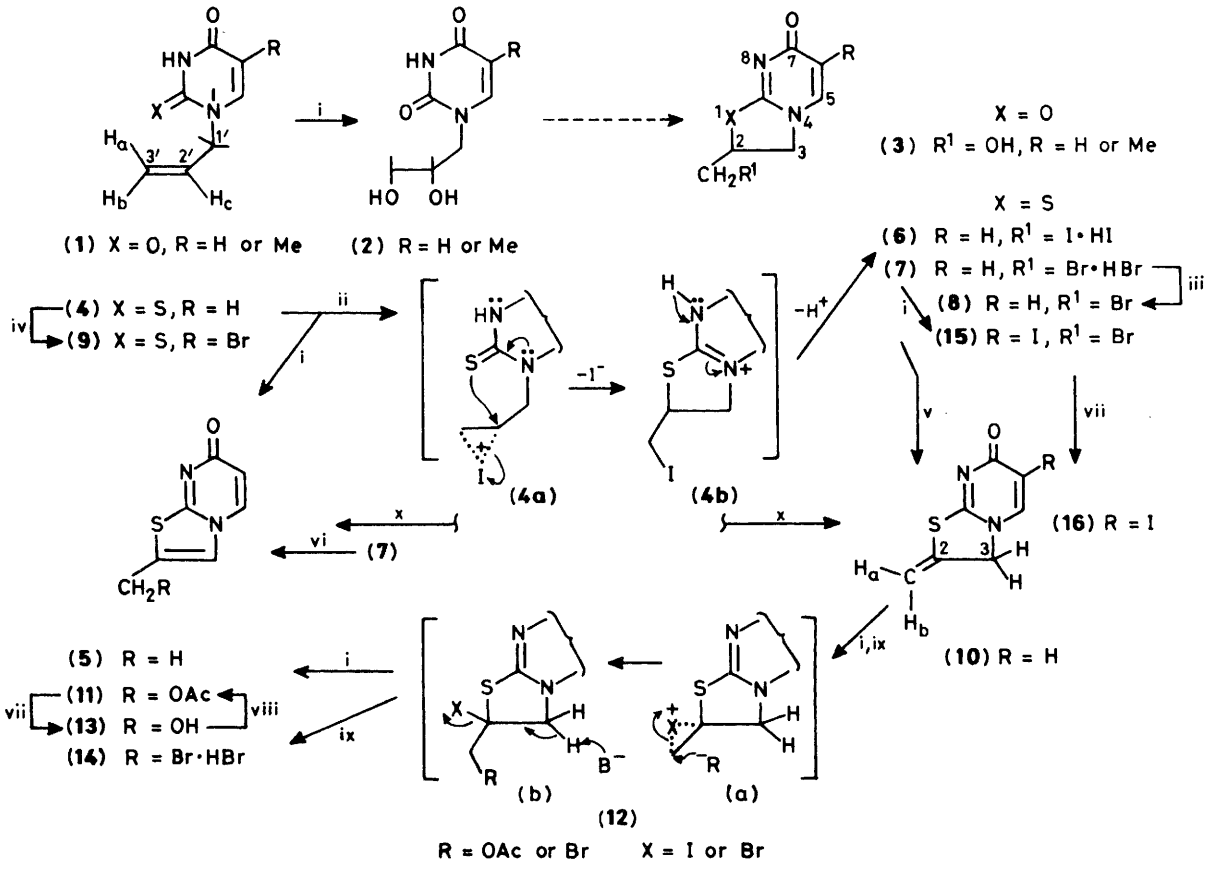
It is interesting to note that the bromination of (**4**) with an equimolar amount of *N*-bromosuccinimide[8] in refluxing CCl_4 afforded 1-allyl-5-bromo-2-thiouracil (**9**) in high yield, possibly as a result of a low and insufficient concentration of the generated Br_2 for an addition reaction. The product (**9**) showed ^{1}H n.m.r. spectral characteristics for the allylic part of the molecule which were similar to those of compound (**4**).

To gain a deeper insight into the formation of the fully aromatic thiazolo[3,2-*a*]pyrimidin-7-one (**5**), the presumed intermediacy of 2-iodo-(bromo-)methyl compounds (**6**) and (**7**) was further investigated. Thus, reaction of (**7**) with AgOAc only in refluxing AcOH was shown to produce (**5**). It was particularly noteworthy that the t.l.c. on silica gel plates revealed besides the main product (**5**) (84%) a more mobile fraction (14.5%), identified as 2,3-dihydro-2-methylene-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**10**). The structure of the latter was unambiguously proved by synthesis from the 2-halogenomethyl derivatives (**6**) and (**7**) in reactions with bases (KOH–EtOH or NaOMe–MeOH). In this synthesis, the appearance of the 2-methyl isomer (**5**) was also observed, but as a minor component. This could be interpreted in terms of lower (**10**)→(**5**) double-bond migration tendencies under basic rather than under acidic conditions. In order to prove this deduction, we treated compound (**10**) with equimolar amounts of AgOAc and HBr in refluxing AcOH to obtain compound (**5**) in 79% yield.

The structural elucidation of (**10**) was straightforward, since its C-2 methylene protons in the ^{1}H n.m.r. spectrum appeared at δ 5.38 and 4.93 as two double doublets, and C-3 geminal protons at δ 4.28 as characteristic doublets with allylic couplings (*J* 2.2 and 1.95 Hz). Moreover, the treatment of the 2-methylene compound (**10**) with I_2–AgOAc in refluxing AcOH afforded 2-acetoxymethyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**11**), apparently *via* an iodonium ion (**12a**; X = I, R = OAc) and a 2-acetoxymethyl-2-iodo adduct (**12b**; X = I, R = OAc) as intermediates, in accordance with Woodward's oxidation procedure.[5] The ^{1}H n.m.r. spectrum of (**11**) revealed a downfield shift of the C-3 proton (at δ 7.46) and a singlet at δ 2.07 for the acetoxy group. This compound on reaction with NaOMe in MeOH underwent hydrolysis to yield 2-hydroxymethyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**13**), exhibiting a triplet at δ 5.69 (*J* 5.6 Hz) for the primary OH and a singlet at δ 7.19 for the C-3 proton.

We also conducted the bromination of (**10**) into 2-bromomethyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one hydrobromide (**14**). In this case, the intermediate bromonium ion (**12a**; X = R = Br) and the 2-bromomethyl-2-bromo adduct (**12b**; X = R = Br) underwent dehydrobromination. The ^{1}H n.m.r. signals of (**14**) were comparable with those of the 2-acetoxymethyl derivative (**11**).

On the I_2–AgOAc oxidation of the allyl compound (**4**) there was no 2-acetoxymethyl bicyclic product (**11**), arising from the intermediary 2-methylene compound (**10**). This could be explained by the consumption of I_2 during the formation of the 2′,3′-iodonium ion (**4a**) and its conversion into the bicyclic compound (**6**) by an internal highly nucleophilic C-2 sulphur



Reagents: i, I_2–AgOAc–AcOH; ii, $I_2(Br_2)$–CH_2Cl_2; iii, Na_2CO_3–H_2O; iv, NBS–CCl_4; v, KOH–EtOH (NaOMe–MeOH); vi, AgOAc–AcOH; vii, NaOMe–MeOH; viii, $(Ac)_2O$–py; ix, Br_2–CH_2Cl_2; x, HBr–AgOAc–AcOH

atom[9] attack at the C-2′ position rather than an acetate ion attack.

Treatment of 2-bromomethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one hydrobromide (**7**) with an equimolar amount of I_2–AgOAc in refluxing AcOH led to 2-bromomethyl-2,3-dihydro-6-iodo-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**15**), which was formed in 65% yield, as the product of a C-6 substitution. The structure of the latter was evidenced by the ^1H n.m.r. spectrum, in good accordance with the spectra of (**6**), (**7**), and (**8**), and by dehydrobromination into 2,3-dihydro-6-iodo-2-methylene-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**16**) by NaOMe in MeOH. The structure revealed two sets of resonances at δ 5.55 and 4.95 for C-2 methylene protons, and doublets at δ 4.28 for C-3 geminal protons with characteristic allylic couplings (*J* 2.2 and 1.95 Hz). It is worth noting that the 2-bromomethyl compound (**7**) in refluxing AcOH remained unchanged.

In conclusion, the data reported above supported the I_2–AgOAc transformation of 1-allyl-2-thiouracil (**4**) into 3-methylthiazolo[3,2-*a*]pyrimidin-7-one (**5**) *via* a sequence of iodination, intramolecular 2,2′-cyclisation, dehydroiodination, and double-bond migration processes. In addition, the final transformations, especially double-bond migration, proceeded in the presence of either HI or AgI, being generated during the cyclisation and dehydroiodination processes. Further studies of the role of HI (or possible AgI) in AcOH in the transformations mentioned above, especially in comparison with those of silver salt catalysts,[10] are necessary for a better understanding of presumed proton-transfer reactions.

Experimental

Melting points, uncorrected, were taken on a Kofler hot-stage. I.r. spectra were obtained for potassium bromide pellets on a Perkin-Elmer 297 spectrophotometer. U.v. spectra were taken for a solution in EtOH with a Perkin-Elmer 124 spectrophotometer. ^1H N.m.r. spectra were measured for solutions in $(CD_3)_2SO$ on a JEOL JNM-FX 100 FT-NNM spectrometer with $SiMe_4$ as the internal standard unless otherwise stated. The silica gel (Merck HF_{254}, type 60) for t.l.c. and for preparative t.l.c. was activated at 110 °C for 60 min. The products were developed and recovered in CH_2Cl_2–MeOH (9:1) unless otherwise stated, and rendered visible by u.v. illumination.

1-*Allyl*-1,2-*dihydro*-2-*thioxopyrimidin*-4(3H)-*one* (1-*Allyl*-2-*thiouracil*) (**4**).—To a solution of anhydrous 2-thiouracil (1.28 g, 10 mmol) in DMF (0.4 ml), hexamethyldisilazane (HMDS) (6 ml) was added. The mixture was heated at 150 °C for 15 h and then cooled, treated with solution of allyl bromide (2 ml, 22 mmol) in MeCN (20 ml), and then set aside at room temperature for 4 days. The solvent and excess of HMDS were removed under reduced pressure at 35 °C. The residue was dissolved in anhydrous MeOH (20 ml) and neutralized with 1.0 mol dm^{-3} methanolic KOH. This solution was then evaporated to dryness and triturated with $CHCl_3$. The precipitate was filtered off and the filtrate partitioned with water. The $CHCl_3$ extract was dried and evaporated to a crystalline product (698 mg, 83%), R_F *ca.* 0.74, m.p. 136—137 °C (from EtOAc) (Found: C, 50.1; H, 4.9; N, 16.5. $C_7H_8N_2OS$ requires C, 50.0; H, 4.8; N, 16.7%); $\lambda_{max.}$ 224 and 287 nm (log ε 4.08 and 3.95); $\lambda_{infl.}$ 240 nm (log ε 3.96); $\lambda_{min.}$ 212 and 258 nm (log ε 3.99 and 3.70); $\nu_{max.}$ 3 480br, 3 080, 3 035, 2 928, 2 880br, 1 695, 1 687, 1 683, 1 678, 1 675, 1 639, 1 627, 1 578, 1 574, 1 550, and 1 539 cm^{-1}; δ($CDCl_3$) 7.87 (1 H d, 6-H, $J_{6,5}$ 6.6 Hz), 6.24 (1 H, d, 5-H, $J_{5,6}$ 6.5 Hz), 5.94 (1 H, ddt, 2′-H_c, $J_{2'c,3'a}$ 16.8, $J_{2'c,3'b}$ 9.5, $J_{2',1'}$ 6.8 Hz), 5.31 (1 H, ddd, 3′-H_a, $J_{3'a,2'c}$ 16.8, $J_{a,b}$ 3.0 and $J_{a,1'}$ 1.5 Hz), 5.11

(1 H, ddd, 3'-H_b, $J_{3'b,2'c}$ 9.5, $J_{b,a}$ 3.0 and $J_{b,1'}$ 1.5 Hz), and 3.85 (2 H, d, 1'-H_2, $J_{1',2'}$ 6.8 Hz).

2-*Methyl*-7H-*thiazolo*[3,2-a]*pyrimidin*-7-*one* (**5**).—To a solution of 1-allyl-2-thiouracil (**4**) (366 mg, 2 mmol) in glacial AcOH (10 ml) I_2 (513 mg, 2.1 mmol) and AgOAc (751 mg, 4.5 mmol) were added. To this suspension, which was stirred for 30 min, 99% AcOH (5 ml) was added and the whole then heated under reflux for an additional 6 h. After NaCl had been added a precipitate was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was triturated with anhydrous MeOH (40 ml) to remove further precipitate. The final filtrate was evaporated and the resulting residue neutralized with 1% methanolic KOH; it was then treated with additional 2.2% methanolic KOH (20 ml) and the whole stirred at room temperature for 18 h. This solution was neutralized with 2 mol dm^{-3} HCl. The precipitate was filtered off and the filtrate evaporated to leave a residue which was purified by preparative t.l.c. (recovery with CH_2Cl_2–MeOH, 8:2). Besides several by-products (four fractions, 33 mg) the products, R_F *ca.* 0.48, separated in 73.2% (243 mg) yield, m.p. 250—251 °C (from MeOH–Et_2O) (Found: C, 50.8; H, 3.7; N, 16.6. $C_7H_6N_2OS$ requires C, 50.55; H, 3.65; N, 16.85%); $\lambda_{max.}$ 223, 230, and 275 nm (log ε 3.55, 3.51, and 3.47); $\lambda_{min.}$ 217 and 244 nm (log ε 3.54 and 2.92); $\nu_{max.}$ 3 420br, 3 058, 3 020, 2 968, 2 924, 1 667, 1 642sh, 1 628, 1 612, and 1 592 cm^{-1}; δ 8.23 (1 H, d, 5-H, $J_{5,6}$ 7.7 Hz), 6.96 (1 H, s, with secondary splitting, 3-H, *J* 1.2 Hz), 6.22 (1 H, d, 6-H, $J_{6,5}$ 7.7 Hz), 2.34 (3 H, s, with secondary splitting, 2-Me, *J* 1.2 Hz).

Treatment of 1-*Allyl*-2-*thiouracil* (**4**) *with Acetic Acid.*—A solution of 1-allyl-2-thiouracil (**4**) (84 mg, 0.5 mmol) in glacial AcOH (5 ml) was heated under reflux for 24 h and the mixture then evaporated to dryness under reduced pressure. Preparative t.l.c. separated the starting material (39 mg) at R_F *ca.* 0.66 and a fraction at R_F *ca.* 0.23, which was identified as 2-thiouracil (27 mg, 85%), based on the transformed starting material, m.p. >311 °C, identical (mixed m.p. and i.r. spectrum) with an authentic sample; δ 10.93br (2 H, s, 1-NH and 3-NH), 7.38 (1 H, d, 6-H, $J_{6,5}$ 7.6 Hz), 5.45 (1 H, d, 5-H, $J_{5,6}$ 7.6 Hz).

2-*Iodomethyl*-2,3-*dihydro*-7H-*thiazolo*[3,2-a]*pyrimidin*-7-*one Hydroiodide* (**6**).—To a solution of 1-allyl-2-thiouracil (**4**) (302.4 mg, 1.8 mmol) in CH_2Cl_2 (80 ml), protected from moisture and light, I_2 (455.4 mg, 2.2 mmol), dissolved in CH_2Cl_2 (25 ml), was added dropwise and the mixture heated under reflux for 10 h. The product was separated by suction; yield 600 mg (79%), R_F *ca.* 0.42, m.p. 186—187 °C (from MeOH–Et_2O) (Found: C, 19.9; H, 2.15; N, 6.55. $C_7H_7IN_2OS$·HI requires C, 19.9; H, 1.9; N, 6.65%); $\lambda_{max.}$ 226 and 260 nm (log ε 4.52 and 3.99); $\lambda_{min.}$ 203 nm (log ε 4.06); $\nu_{max.}$ 3 509br, 3 333sh, 3 096, 2 933, 1 708, 1 681, 1 634, 1 600sh, 1 524, and 1 504 cm^{-1}; δ 8.08 (1 H, d, 5-H, $J_{5,6}$ 7.9 Hz), 6.2 (1 H, d, 6-H, $J_{6,5}$ 7.9 Hz), 5.06—4.75 (1 H, m, 2-H), 4.2br (protonated species), 3.91 (1 H, dd, 3-H_b, $J_{b,a}$ 11.9 Hz, $J_{b,2}$ 8.5 Hz), 3.80—3.67 (2 H, m, 2-CH_2I), and 3.40 (1 H, dd, 3-H_a $J_{a,b}$ 11.9, $J_{a,2}$ 4.6 Hz).

2-*Bromomethyl*-2,3-*dihydro*-7H-*thiazolo*[3,2-a]*pyrimidin*-7-*one Hydrobromide* (**7**).—To a solution of 1-allyl-2-thiouracil (**4**) (304 mg, 1.8 mmol) in CH_2Cl_2 (80 ml), protected from moisture, anhydrous Br_2 in CH_2Cl_2 (0.5:100 v/v; 22 ml, 2.2 mmol) was added dropwise and the mixture stirred at room temperature for 3 h. The product was separated by suction; yield 560 mg (94%), R_F *ca.* 0.48, m.p. 215—216 °C (from MeOH) (Found: C, 25.6; H, 2.2; N, 8.8. $C_7H_7BrN_2OS$·HBr requires C, 25.65; H, 2.55; N, 8.55%); $\lambda_{max.}$ 233 nm (log ε 4.32); $\lambda_{infl.}$ 265 nm (log ε 3.75); $\lambda_{min.}$ 208 nm (log ε 3.55); $\nu_{max.}$ 3 440br, 3 116, 3 095, 3 055, 2 962, 1 726, 1 716, 1 708, 1 703, 1 682, 1 638, 1 536, and 1 507 cm^{-1}; δ 8.08 (1 H, d, 5-H, $J_{5,6}$ 7.8 Hz), 6.14 (1 H, d, 6-H, $J_{6,5}$ 7.8 Hz), 5.23—5.05 (1 H, m, 2-H), 4.77br (protonated species), 4.06—3.93 (2 H, m, 2-CH_2Br), 3.9 (1 H, dd, 3-H_b, $J_{b,a}$ 11.7 and $J_{b,2}$ 8.3 Hz), 3.46 (1 H, dd, 3-H_a, $J_{a,b}$ 11.7, $J_{a,2}$ 4.4 Hz).

2-*Bromomethyl*-2,3-*dihydro*-7H-*thiazolo*[3,2-a]*pyrimidin*-7-*one* (**8**).—A solution of the hydrobromide (**7**) (28.6 mg, 0.1 mmol) in MeOH (2 ml) was treated with Na_2CO_3·$10H_2O$ (32.8 mg, 0.1 mmol), dissolved in water (1 ml). The mixture was stirred for 5 min and the precipitate was filtered off. The filtrate was evaporated to give an unstable oil; δ 7.91 (1 H, d, 5-H, $J_{5,6}$ 7.6 Hz), 5.89 (1 H, d, 6-H, $J_{6,5}$ 7.6 Hz), 5.18—4.93 (1 H, m, 2-H), 4.04—3.92 (2 H, m, 2-CH_2Br), 3.82 (1 H, dd, 3-H_b, $J_{b,a}$ 11.8 and $J_{b,2}$ 8.2 Hz), 3.37 (1 H, dd, 3-H_a, $J_{a,b}$ 11.8 and $J_{a,2}$ 4.4 Hz).

1-*Allyl*-5-*bromo*-2-*thiouracil* (**9**).—To a solution of 1-allyl-2-thiouracil (**4**) (84 mg, 0.5 mmol) in anhydrous CCl_4 (20 ml) *N*-bromosuccinimide (NBS) (75 mg, 0.5 mmol) was added. The mixture was refluxed for 6 h and then filtered. The filtrate was evaporated to give a crystalline product (106 mg, 86%), R_F *ca.* 0.5 ($CHCl_3$–MeOH, 100:2), m.p. 160—162 °C (from benzene–hexane) (Found: C, 34.25; H, 3.15; N, 11.25. $C_7H_7BrN_2OS$ requires C, 34.0; H, 2.85; N, 11.35%); $\lambda_{max.}$(MeOH) 222 and 298 nm (log ε 3.94 and 3.97); $\lambda_{infl.}$ 246 and 324 nm (log ε 3.86 and 3.57); $\lambda_{min.}$ 240 and 267 nm (log ε 3.86 and 3.57); $\nu_{max.}$ 3 450br, 3 198, 3 018, 2 919, 2 818br, 1 673sh, 1 668sh, 1 651br, 1 637sh, 1 561, 1 558, and 1 528br cm^{-1}; δ($CDCl_3$) 8.13 (1 H, s, 6-H), 5.93 (1 H, dddt, 2'-H_c, $J_{2'c,3'a}$ 16.6, $J_{2'c,3'b}$ 9.7, and $J_{2',1'}$ 6.6 Hz), 5.33 (1 H, ddd, 3'-H_a, $J_{3'a,2'c}$ 16.6, $J_{a,b}$ 2.8 and $J_{a,1'}$ 1.2 Hz), 5.15 (1 H, ddd, 3'-H_b, $J_{3'a,2'c}$ 9.5, $J_{b,a}$ 2.8 and $J_{b,1'}$ 1.2 Hz), 3.84 (2 H, d, 1'-H_2, $J_{1',2'}$ 6.8 Hz).

2,3-*Dihydro*-2-*methylene*-7H-*thiazolo*[3,2-a]*pyrimidin*-7-*one* (**10**).—(*a*) 2-Bromomethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]-pyrimidin-7-one hydrobromide (**7**) (328 mg, 1 mmol) was dissolved in hot anhydrous EtOH (100 ml) and then treated with ethanolic 0.1 mol dm^{-3} KOH (21 ml). This mixture was heated under reflux for 30 min and then evaporated to dryness under reduced pressure. The residue was triturated with $CHCl_3$ and the precipitate filtered off. The filtrate was evaporated to leave a mixture of two components which were subjected to preparative t.l.c. (two developments). The product (**10**), R_F *ca.* 0.63, was separated in 68.7% (114 mg) yield, m.p. 271—273 °C (from CH_2Cl_2–Et_2O) (Found: C, 50.5; H, 3.8; N, 16.95. $C_7H_6N_2OS$ requires C, 50.6; H, 3.65; N, 16.85%); $\lambda_{max.}$ 247 and 283 nm (log ε 3.82 and 3.52); $\lambda_{min.}$ 270 nm (log ε 3.49); $\nu_{max.}$ 3 460br, 3 101, 3 020, 2 974, 1 662, 1 660, 1 650, 1 640, 1 637, 1 609, and 1 594 cm^{-1}; δ 8.24 (1 H, d, 5-H, $J_{5,6}$ 7.8 Hz), 6.0 (1 H, d, 6-H, $J_{6,5}$ 7.8 Hz), 5.38 (1 H, dd, 2-CH_a, $J_{a,b}$ 3.9, $J_{a,3}$ 2.2 Hz), 4.93 (1 H, dd, 2-CH_b, $J_{b,a}$ 3.9, $J_{b,3}$ 1.95 Hz), 4.28 (2 H, dd, 3-H_2, $J_{gem.}$ 2.1, $J_{3,a}$ 2.2, $J_{3,b}$ 1.95 Hz).

The fraction, R_F *ca.* 0.48, was identified as 2-methyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**5**) (50 mg, 30%), m.p. 250—251 °C (from MeOH–Et_2O), identical (mixed m.p. and i.r. and ^1H n.m.r. spectra) with an authentic sample.

(*b*) 2-Iodomethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one hydroiodide (**6**) (211 mg, 0.5 mmol) was dissolved in hot anhydrous EtOH (50 ml), treated with ethanolic 0.1 mol dm^{-3} KOH (16 ml), and then heated under reflux for 1 h. The mixture was worked up as described under (*a*). The preparative t.l.c. afforded the product (**10**), R_F *ca.* 0.63, in 67% (54.3 mg) yield, m.p. 271—273 °C and 2-methyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**5**) (20 mg, 24%), R_F *ca.* 0.48, m.p. 249—251 °C, which were identical (mixed m.p. and i.r. and ^1H n.m.r. spectra) with those obtained under (*a*).

(*c*) 2-Bromomethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one hydrobromide (**7**) (328 mg, 1 mmol) was dissolved in MeOH (15 ml) and treated with methanolic

NaOMe (0.1 mol dm^{-3}; 9.5 ml, 1 mmol). The mixture was then stirred at room temperature for 2 h and worked up as described under (*a*). The product (**10**), R_F *ca.* 0.63 was isolated in 60.2% (100 mg) yield and the by-product (**5**), R_F *ca.* 0.48 in 34.4% (57 mg) yield, identical (mixed m.p. and i.r., ^1H n.m.r. spectra) with those under (*a*).

Treatment of 2-*Bromomethyl*-2,3-*dihydro*-7H-*thiazolo*[3,2-a]-*pyrimidin*-7-*one Hydrobromide* (**7**) *with Silver Acetate in Acetic Acid*.—To a solution of thiazolo[3,2-*a*]pyrimidin-7-one hydrobromide (**7**) (82 mg, 0.25 mmol) in glacial AcOH (5 ml) AgOAc (94 mg, 0.56 mmol) was added. The suspension was heated under reflux for 5 h. A precipitate was filtered off and the filtrate evaporated to dryness under reduced pressure. Preparative t.l.c. separated two components at R_F *ca.* 0.48 and *ca.* 0.63. The fraction, R_F *ca.* 0.48, was isolated in 84.3% (35 mg) yield, m.p. 249—251 °C and identified as 2-methyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**5**), identical (mixed i.r. and ^1H n.m.r. spectra) with an authentic sample. The fraction, R_F *ca.* 0.63, was identified as 2,3-dihydro-2-methylene-7*H*-thiazolo[3,2-*a*]-pyrimidin-7-one (**10**) (6 mg, 14.5%), m.p. 269—272 °C, identical (mixed m.p., i.r. and ^1H n.m.r. spectra) with an authentic sample.

2-*Acetoxymethyl*-7H-*thiazolo*[3,2-a]*pyrimidin*-7-*one* (**11**).—(*a*) A solution of 2-methylene-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**10**) (83 mg, 0.5 mmol) in glacial AcOH (12 ml) was treated with AgOAc (207 mg, 1.2 mmol) and I_2 (150 mg, 0.58 mmol) for 30 min at room temperature and then heated under reflux for 6 h. The mixture was then evaporated to dryness under reduced pressure and the residue triturated with acetone. The precipitate was filtered off and the excess of Ag ion removed from the filtrate by precipitation with H_2S. The product (72 mg, 63.7%) was purified by preparative t.l.c., R_F *ca.* 0.51, m.p. 193—195 °C (from acetone–hexane) (Found: C, 48.3; H, 3.9; N, 12.3. $C_9H_8N_2O_3S$ requires C, 48.2; H, 3.6; N, 12.5%); $\lambda_{max.}$ 218 and 273 nm (log ε 4.27 and 3.61); $\lambda_{infl.}$ 230 nm (log ε 4.14); $\lambda_{min.}$ 244 nm (log ε 4.07); $\nu_{max.}$ 3 436br, 3 040, 1 742, 1 656, 1 639, 1 626, and 1 600br cm^{-1}; δ 8.32 (1 H, d, 5-H, $J_{5,6}$ 7.8 Hz), 7.46 (1 H, s, 3-H), 6.28 (1 H, d, 6-H, $J_{6,5}$ 7.8 Hz), 5.20 (2 H, s, 2-CH_2O), and 2.07 (3 H, s, COMe).

(*b*) 2-Hydroxymethyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**13**) (45.5 mg, 0.25 mmol) was treated with acetic anhydride (0.5 mmol) and pyridine (1 ml) at room temperature for 2 h. The mixture was evaporated to dryness under reduced pressure. The crystalline product was obtained on trituration with ether (54 mg, 95.4%), m.p. 193—195 °C, identical (mixed m.p. and i.r. and ^1H n.m.r. spectra) with that described under (*a*).

2-*Hydroxymethyl*-7H-*thiazolo*[3,2-a]*pyrimidin*-7-*one* (**13**).—To a solution of 2-acetoxymethyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**11**) (113 mg, 0.5 mmol) in anhydrous MeOH (15 ml) NaOMe (0.1 mol dm^{-3}; 0.5 mmol) was added. The mixture was stirred at room temperature for 30 min. The crystalline product was separated by suction and washed with ether; yield 76 mg (74%), R_F *ca.* 0.45, m.p. 250—253 °C (from MeOH) (Found: C, 46.05; H, 3.05; N, 15.45. $C_7H_6N_2O_2S$ requires C, 46.15; H, 3.3; N, 15.4%); $\lambda_{max.}$ 217 and 274 nm (log ε 4.13 and 3.77); $\lambda_{infl.}$ 231 nm (log ε 3.91); $\lambda_{min.}$ 244 nm (log ε 3.26); $\nu_{max.}$ 3 460br, 3 197br, 3 068, 1 670sh, 1 660sh, 1 640sh, 1 625, and 1 590br cm^{-1}; δ 8.24 (1 H, d, 5-H, $J_{5,6}$ 7.8 Hz), 7.19 (1 H, s, 3-H), 6.24 (1 H, d, 6-H, $J_{6,5}$ 7.8 Hz), 5.69 (1 H, t, OH), $J_{OH,2\text{-}CH_2}$ 5.6 Hz), and 4.58 (2 H, d, 2-CH_2O, $J_{2\text{-}CH_2,OH}$ 5.6 Hz).

2-*Bromomethyl*-7H-*thiazolo*[3,2-a]*pyrimidin*-7-*one Hydrobromide* (**14**).—To a solution of 2-methylenethiazolopyrimidin-7-one (**10**) (166 mg, 1 mmol) in CH_2Cl_2 (50 ml) protected from moisture, anhydrous Br_2, dissolved in CH_2Cl_2 (0.5:100 v/v; 13 ml, 1.3 mmol) was added dropwise and stirred at room temperature for 5 h. The acidic product separated by suction; yield 300 mg (92%), R_F *ca.* 0.56, m.p. 256—262 °C (from MeOH–Et_2O) (Found: C, 26.0; H, 2.1; N, 8.7. $C_7H_5BrN_2OS$·HBr requires C, 25.8; H, 1.85; N, 8.6%); $\lambda_{max.}$ 224 and 274 nm (log ε 4.92 and 4.26); $\lambda_{min.}$ 245 nm (log ε 4.05); $\nu_{max.}$ 3 085, 2 996, 2 945, 2 545br, 1 765sh, 1 702, 1 675, 1 627, and 1 596 cm^{-1}; δ 8.67 (1 H, d, 5-H, $J_{5,6}$ 7.8 Hz), 7.85 (1 H, s, 3-H), 6.75 (1 H, d, 6-H, $J_{6,5}$ 7.8 Hz), 5.64br (protonated species), and 5.08 (2 H, s, 2-CH_2Br).

2-*Bromomethyl*-2,3-*dihydro*-6-*iodo*-7H-*thiazolo*[3,2-a]-*pyrimidin*-7-*one* (**15**).—To a solution of 2-bromomethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one hydrobromide (**7**) (328 mg, 1 mmol) in glacial AcOH (15 ml) AgOAc (376 mg, 2.25 mmol) was added. The mixture was then treated with I_2 (265 mg, 1.05 mmol) during 30 min and heated under reflux for an additional 5 h. A precipitate formed and this was filtered off and the filtrate evaporated to a residue, which on recrystallization from MeOH afforded the product (242 mg, 64.9%), R_F *ca.* 0.6, m.p. 197—200 °C (Found: C, 22.7; H, 1.65; I, 33.95; N, 7.4. $C_7H_6BrIN_2OS$ requires C, 22.55; H, 1.6; I, 34.0; N, 7.5%); $\lambda_{max.}$ 235 nm (log ε 4.25); $\lambda_{infl.}$ 291 nm (log ε 3.84); $\nu_{max.}$ 3 460br, 3 012, 2 905, 1 616, 1 610, and 1 595 cm^{-1}; δ 8.48 (1 H, s, 5-H), 5.18—4.93 (1 H, m, 2-H), 4.04—3.9 (2 H, m, 2-CH_2Br), 3.82 (1 H, dd, 3-H_b, $J_{b,a}$ 11.6 and $J_{b,2}$ 8.5 Hz), and 3.39 (1 H, dd, 3-H_a, $J_{a,b}$ 11.6 and $J_{b,2}$ 4.4 Hz).

2,5-*Dihydro*-6-*iodo*-2-*methylene*-7H-*thiazolo*[3,2-a]-*pyrimidin*-7-*one* (**16**).—A solution of 2-bromomethyl-2,3-dihydro-6-iodo-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**15**) (357 mg, 1 mmol) in anhydrous MeOH (150 ml) was treated with methanolic NaOMe (0.1 mol dm^{-3}; 10 ml). The mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the resulting residue triturated with MeOH. The precipitate was identified as the starting material (130 mg). The filtrate was evaporated to give a foamy product. Preparative t.l.c. (two developments) afforded the product (**16**) (120 mg, 62%, based on the transformed amount of starting material), R_F *ca.* 0.6, m.p. >300 °C (from CH_2Cl_2–hexane) (Found: C, 29.05; H, 1.95; I, 43.55; N, 9.5. $C_7H_5IN_2OS$ requires C, 28.8; H, 1.75; I, 43.45; N, 9.6%); $\lambda_{max.}$ 244 nm (log ε 4.23); $\lambda_{infl.}$ 290 nm (log ε 3.93); $\lambda_{min.}$ 273 nm (log ε 3.91); $\nu_{max.}$ 3 480br, 3 110, 3 009, 1 660, 1 645sh, 1 638, 1 602, 1 580sh, 1 562sh cm^{-1}; δ 8.79 (1 H, s, 5-H), 5.55 (1 H, dd, 2-CH_a, $J_{a,b}$ 4.5, $J_{a,3}$ 2.2 Hz), 4.95 (1 H, dd, 2-CH_b, $J_{b,a}$ 4.5, $J_{b,3}$ 1.95 Hz), 4.27 (2 H, dd, 3-H_2, $J_{gem.}$ 2.1, $J_{3,a}$ 2.2, $J_{3,b}$ 1.95 Hz).

Treatment of 2,3-*Dihydro*-2-*methylene*-7H-*thiazolo*[3,2-a]-*pyrimidin*-7-*one* (**10**) *with Silver Acetate–Hydrobromic Acid in Acetic Acid*.—To a solution of 2-methylenethiazolo[3,2-*a*]-pyrimidin-7-one (**10**) (40 mg, 0.25 mmol) in glacial AcOH (3 ml) 63% HBr (0.033 ml, 0.25 mmol) was added. The suspension thus formed was treated with AgOAc (40 mg, 0.25 mmol), and the whole heated under reflux for 3 h; it was then set aside at room temperature for 16 h. The resulting precipitate was filtered off and the filtrate evaporated to dryness. The residue was recrystallized from MeOH–Et_2O, R_F *ca.* 0.48, and identified as 2-methyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**5**) (30 mg, 75%), m.p. 249—251 °C, identical (mixed m.p., i.r. and ^1H n.m.r. spectra) with an authentic sample.

References

1 V. Škarić and M. Jokić, *Croat. Chem. Acta*, 1983, **56**, 125.
2 V. Škarić, Z. Raza, and D. Škarić, *J. Chem. Soc., Perkin Trans. 1*, 1982, 223.
3 V. Škarić, D. Erben, Z. Raza, and D. Škarić, *Croat. Chem. Acta*, 1979, **52**, 281.

4 V. Škarić and Z. Raza, *Croat. Chem. Acta*, 1979, **52**, 51.
5 R. B. Woodward and F. V. Brutcher Jr., *J. Am. Chem. Soc.*, 1958, **80**, 209.
6 S. R. Naik, J. T. Witkowski, and R. K. Robins, *J. Heterocycl. Chem.*, 1974, **11**, 575.
7 C. D. Hurd and S. Hayao, *J. Am. Chem. Soc.*, 1955, **77**, 117.
8 K. Ziegler, W. Schumann, and E. Winkelmann, *Liebigs Ann. Chem.*, 1942, **551**, 120.
9 G. Stork and A. Schoofs, *J. Am. Chem. Soc.*, 1979, **101**, 5081.
10 D. N. Kevill and C. R. Degenhardt, *J. Am. Chem. Soc.*, 1979, **101**, 1465.

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