Studies on the Chemistry of 5-Propynyloxy- and 5-Propynylthiopyrimidines: New Syntheses of Furo- and Thieno[3,2-*d*]pyrimidines

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The utility of certain 5-alkynyloxy-, 5-alkynylthio-, and 5-alkynylsulfinyl-pyrimidines as precursors of 7-substituted furo[3,2-*d*]- and thieno[3,2-*d*]pyrimidines has been examined. When treated with sodium methoxide in warm methyl sulfoxide, 1,3-dimethyl-5-(2-propynyloxy)uracil (**6**) cyclizes to afford 1,3,7-trimethylfuro[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**12**) in 52% yield, possibly *via* the allenic ether **9** (R = H). The corresponding 5-(2-butynyloxy)pyrimidine (**7**), obtained in good yield by treating **6** with methyl iodide and sodium hydride in methyl sulfoxide, fails to undergo an analogous cyclization. However, compound **7** does undergo a normal alkynyl Claisen rearrangement and cyclization when heated at 130°, giving the 8-methylpyrano[3,2-*d*]pyrimidine **8** in methyl sulfoxide and the 6,7-dimethylfuro[3,2-*d*]pyrimidine **11** in dimethylformamide. The 5-(2-propynylthio)pyrimidine **15** affords the allene **19** and the 1-propyne **22** when treated with various bases, but none of the 7-methylthieno[3,2-*d*]pyrimidine **16**. At 145° in methyl sulfoxide, **15** undergoes a thio-Claisen rearrangement process to afford the 6-methylthieno[3,2-*d*]pyrimidine **17** together with substantial amounts of a product **20** that bears a 7-thiomethoxymethyl substituent derived from the solvent. Heating the 5-(2-propynylsulfinyl)pyrimidine **23** at 105° in methyl sulfoxide, followed by acidification of the reaction mixture, affords 1,3-dimethyl-7-formylthieno[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**29**) in 47% yield. Deuterium labelling studies established that the aldehyde proton of **29** is derived from the 3'-proton of **23**. This finding is consistent with a mechanism that involves sequential [2,3] and [3,3] sigmatropic rearrangements, and the intermediacy of a dihydrothieno[3,2-*d*]pyrimidine such as compound **30**.

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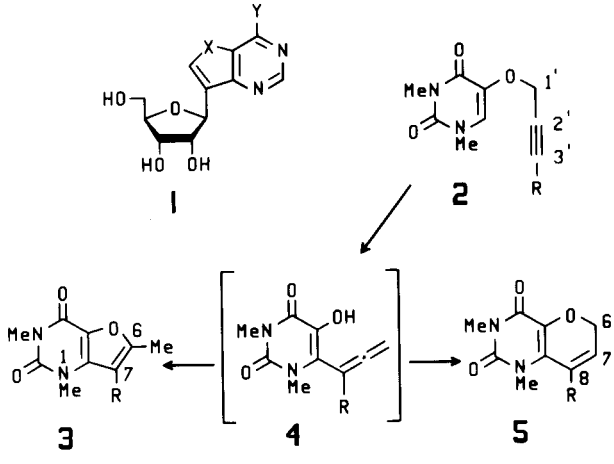
During our studies with synthetic bicyclic *C*-nucleosides such as **1** (Scheme 1), it has become apparent that compounds containing the thieno[3,2-*d*]pyrimidine (X = S) [1] and furo[3,2-*d*]pyrimidine (X = O) [2] ring systems can function as purine antimetabolites. As a result, they elicit a variety of biological effects, including *in vitro* antitumor activity for the adenosine analogues (**1**, Y = NH_2, X = S or O) [1a, 2a] and *in vitro* activity against Trypanosoma gambiense for the inosine analogues (**1**, Y = OH, X = S or O) [1c, 2b]. In view of these results, we have become interested in examining additional methods for the synthesis of furo- and thieno[3,2-*d*]pyrimidines, with particular emphasis on finding approaches that could be adapted for the synthesis of *C*-nucleosides related to **1**. In the present paper, we report the results of some exploratory studies on the cyclization reactions of certain 5-(2-propynyloxy)-, 5-(2-propynylthio)- and 5-(2-propynylsulfinyl)pyrimidines.

We showed a number of years ago [3] that the propynyloxypyrimidine **2** (R = H) readily undergoes a Claisen rearrangement when heated at 130°. Depending upon the solvent used, the resulting allene **4** (R = H) can cyclize *via* an ionic mechanism to give the furo[3,2,-*d*]pyrimidine **3** (R = H), or it can undergo further sigmatropic rearrangement and cyclization to give the isomeric pyrano[3,2-*d*]-pyrimidine **5** (R = H). In order to explore the scope of these reactions, we wanted to determine whether 3'-substituted derivatives of **2** would rearrange thermally to afford the corresponding 7-substituted-6-methylfuro-[3,2-*d*]pyrimidines. Although suitable 3'-substituted derivatives could probably be made by *O*-alkylation of the parent 5-hydroxypyrimidine, we chose instead to investigate the direct *C*-alkylation approach shown in Scheme 2. Using methyl iodide under a variety of alkaline conditions, it quickly became clear that while **6** can indeed be methylated to give **7**, the course of the reaction is markedly dependent upon the base-solvent combination. Under the most effective conditions found, namely treatment of **6** in methyl sulfoxide with three equivalents of

SCHEME 1



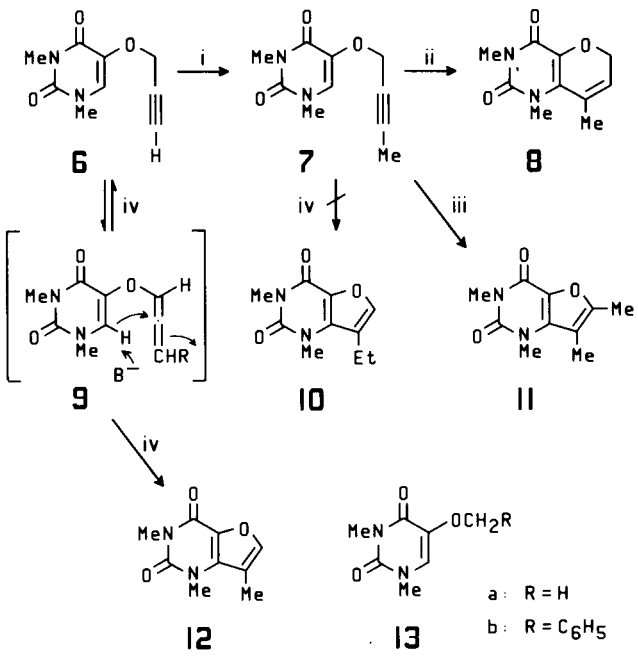
sodium hydride and a large excess of methyl iodide, it was possible to obtain **7** in about 60% yield. Other conditions, such as using smaller amounts of base, or using tetrahydrofuran as solvent, were much less effective.

With **7** on hand, it was a straightforward matter to demonstrate that pyrolysis in methyl sulfoxide at 130° affords mostly the pyrano[3,2-*d*]pyrimidine **8**, whereas heating in dimethylformamide at the same temperature gives the dimethylfuro[3,2-*d*]pyrimidine **11**. The thermal rearrangements of **7** therefore parallel those of **6** [3]. With an appropriately substituted pyrimidine and a carbohydrate moiety comprising the C-3′ substituent, this approach might constitute an interesting route to 6-methylfuro[3,2-*d*]pyrimidine *C*-nucleosides of type **1**. This possibility will be investigated.

We noted above that successful methylation of **6** depends critically on the base-solvent combination used. The reason for this, at least in part, is that **6** itself undergoes an unexpected base-catalyzed cyclization to give the 7-methylfuro[3,2-*d*]pyrimidine **12**. Compound **12** is formed to some extent under the alkylation conditions described above, but it is formed in about 50% yield when **6** is treated with an equivalent amount of sodium methoxide in methyl sulfoxide at 60°. The combination of potassium *t*-butoxide and methyl sulfoxide also affords **12**, although in lower yield, but sodium hydride is less effective, and DBU is without effect, at least at room temperature. In fact, heating methyl sulfoxide solutions of **6** in the presence of DBU affords the 6-methyl isomer **3** (R = H) *via* the thermal rearrangement route (Scheme 1), but none of the 7-methyl isomer **12**. That compound **12** is the 7-methyl isomer follows from a comparison of its nmr spectral properties with those of the 6-methyl isomer **3** (R = H). The downfield shift of the vinylic proton of **12** (δ 7.44) relative to that of **3** (R = H, δ 6.17), as well as the larger one-bond vinylic ^{1}H-^{13}C coupling constant observed for **12** (204 Hz) compared to **3** (R = H, 180 Hz), clearly establishes that the vinyl proton of **12** is adjacent to the furan oxygen atom.

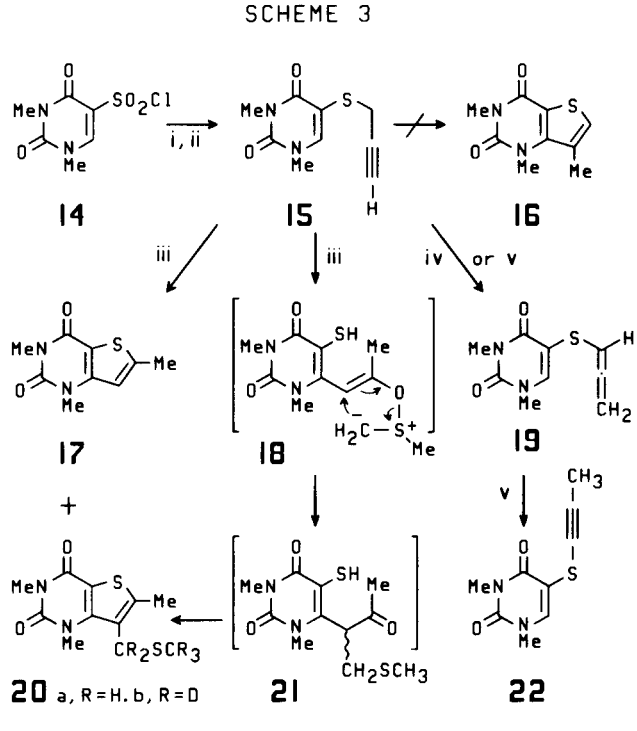
A mechanism that accounts for the formation of **12** from **6** involves an initial isomerization to give the allenic ether **9** (R = H), followed by abstraction of H-6 and cyclization by attack of the C-6 carbanion on the central allene carbon. There are precedents for each of these steps. For example, 2-propynyl ethers are known to isomerize in base to give allenic ethers [4]. Also, examples of cyclizations that involve nucleophilic attack on the central carbon of non-conjugated allenes have been reported [5], although the nucleophile in those cases is a sulfur or nitrogen atom rather than a carbanion. As to the abstraction of H-6, we have already reported [3] that **6** readily undergoes base-catalyzed exchange of H-6 for deuterium. It is likely that

SCHEME 2



Reagents: i) NaH, DMSO, MeI ii) 130°, DMSO
iii) 130°, DMF iv) NaOMe, DMSO, 60°

SCHEME 3



Reagents: i) Zn, H_2SO_4 ii) NaOH, $HC{\equiv}CCH_2Br$
iii) 145°, DMSO iv) N NaOH v) NaH, THF

the exchange involves direct proton abstraction and it seems to be a general property of 5-*O*-substituted pyrimidines. The 5-methoxy and 5-benzyloxy pyrimidines **13a** and **13b** each undergo very rapid H-6 exchange when treated with sodium deuteroxide in methyl sulfoxide-d_6, so it is reasonable to suppose that H-6 of **9** is similarly abstractable. In an attempt to generate **9** (R = H) under mild conditions, **6** was treated with dilute sodium hydroxide in methyl sulfoxide for 18 hours. Compounds **6** is largely unchanged under these conditions, but the residue obtained after recovery of the bulk of the starting material does exhibit nmr signals that are consistent with the presence of **9** (R = H). However, attempts to separate the minor product from residual **6** by chromatography were not successful.

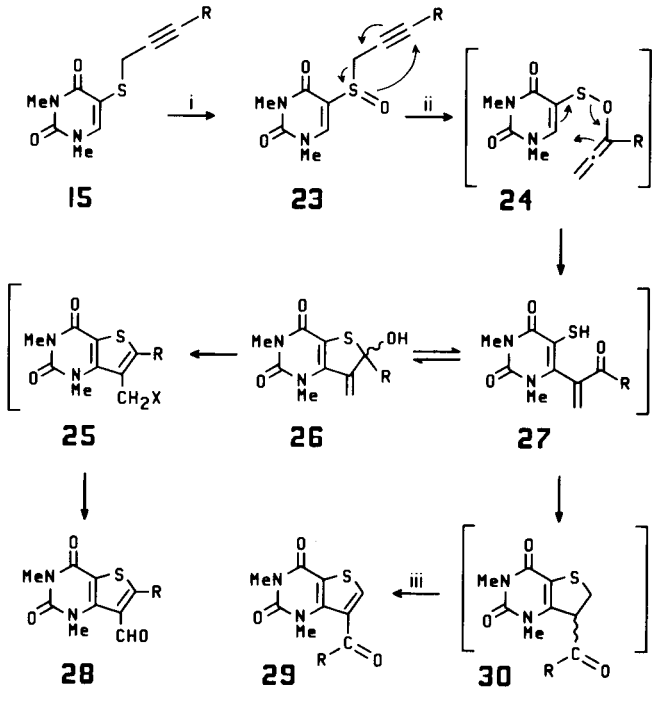
Unfortunately, it appears that the type of cyclization that affords **12** from **6** might be restricted to compounds with unsubstituted 2-propynyloxy groups. Thus, treatment of the butynyl compound **7** with sodium methoxide in methyl sulfoxide at 60° — conditions that convert **6** into **12** — gave no indication that the 7-ethyl product **10** had been formed. In fact, **7** was mostly recovered unchanged and while there was some decomposition, no discrete products were observed. It may be that the formation of an internal allene such as **9** (R = Me) is not favored and it is interesting to note in this regard that, unlike the situation with isomeric terminal allenes and acetylenes, internal acetylenes are significantly lower in energy than their internal allene isomers [5a].

In parallel with the foregoing studies with 5-*O*-substituted pyrimidines, we have also investigated a similar series of reactions with the corresponding 5-thio compounds. The required starting material was prepared by adapting the approach developed by Bardos and co-workers for the synthesis of 5-thiouracil [6]. Thus, 1,3-dimethyluracil was treated with chlorosulfonic acid to afford **14**, (Scheme 3), which was then reduced with zinc and sulfuric acid. Alkylation of the resulting 1,3-dimethyl-5-thiouracil *in situ* with propargyl bromide afforded the desired **15** in moderate overall yield.

When treated with various bases, sulfide **15** undergoes the acetylene-allene isomerization [4] with considerable ease. Simply treating an aqueous suspension of **15** with an equivalent of sodium hydroxide affords the crystalline allene **19** in 78% yield. This product is easily recognized from its nmr spectral properties, in particular the appearance of the characteristic C-2′ allene resonance at 207 ppm in the ^{13}C-spectrum. Under stronger basic conditions, for example sodium hydride in tetrahydrofuran containing a small amount of methyl sulfoxide, **19** undergoes further isomerization to give the internal alkyne **22**. No evidence for the formation of the 7-methylthieno[3,2-*d*]pyrimidine **16** was obtained, which suggests that abstraction of H-6 of **19** does not compete favorably with abstraction of H-1′. With bases such as sodium methoxide, sulfide **15** essentially decomposes to give a multiplicity of products, including 1,3-dimethyluracil.

The 5-(2-propynylthio)uracil **15**, however, undergoes normal Claisen rearrangement and cyclization when heated in dimethylformamide, giving **17** in good yield. The same product is also formed in hot methyl sulfoxide. Unlike the situation with a number of other 2-propynyl sulfides [7,8], no evidence for the formation of the thiopyran product analogous to **5** was obtained. The rearrangement of **15** in methyl sulfoxide also leads to smaller amounts of a product that incorporates a side chain derived from the solvent. This is the methoxythiomethyl compound **20**, which was first obtained in the perdeuterio form **20b** as the rearrangement of **15** was carried out in methyl sulfoxide-d_6 for nmr-monitoring. In the ^{13}C-nmr spectrum of **20b** the C-7 resonance is greatly attenuated relative to C-7 of **20a**. This is consistent with C-7 being the site of the thiomethoxymethyl side chain because the reduction in the number of neighboring protons in **20b** would be expected to result in an increase of the T_1 relaxation time of C-7. Confirmatory evidence was obtained by examining some NOE difference spectra for **20a**. Thus, irradiation of the methylene resonance leads to

SCHEME 4



small positive enhancements of the 1-Me and 6-Me signals; conversely, irradiation of the 1-methyl resonance enhances the methylene signal. The origin of **20** poses some interesting questions. We know that it is not formed directly from **17** because that compound was found to be stable in hot methyl sulfoxide. Similarly, the allene **19**, which could arise from **15** by a thiopropynylic rearrangement [9], does not appear to be a source of **20**, although it does decompose in hot methyl sulfoxide [10]. We suggest that **20** arises from intermediate **18**, which could be formed by attack of methyl sulfoxide on the allene (analogous to **4**) formed by Claisen rearrangement of **15**. A Sommelet-Hauser type of rearrangement on **18** would then afford **21**, which could undergo cyclization and dehydration to give the observed **20**.

A potentially more versatile way of obtaining 7-substituted thieno[3,2-*d*]pyrimidines from 5-(2-propynylthio)-pyrimidines such as **15** is shown in Scheme 4. This approach is based on the conversion of aryl-2-propynylsulfoxides into condensed thiophenes described first by Majumdar and Thyagarajan [11a], and independently by Makisumi and Takada [11b]). A suitable pyrimidine-5-(2-propynylsulfoxide), **23a**, was easily prepared by peracid oxidation of **15a**. Based on these earlier studies [11], we expected that **23a** would undergo thermal rearrangement to give either the dihydro compound **30a** or, in the presence of an added nucleophile X^-, the 7-substituted compound **25a**. These products would arise *via* an initial sigmatropic rearrangement of **23a** to generate the allene **24a**, which would undergo a Claisen-like rearrangement to give the unsaturated aldehyde **27a**. Cyclization of **27a** by Michael addition of the thiol group to the vinylic carbon [11a,b] would then lead to **30a**; alternatively, cyclization to give **26a** followed by an allylic displacement [11b] by X^- would give **25a**. Using methyl sulfoxide as solvent instead of the protic solvents or carbon tetrachloride used by previous investigators, we have found that heating **23a** at 105° for 90 minutes followed by brief treatment with hydrochloric acid affords the aldehyde **29a** instead of **25a** (X = Cl) or **30a** - that is, an unexpected oxidative step occurs somewhere along the pathway. This could involve dehydrogenation of a dihydro intermediate such as **30a**. Alternatively, but perhaps less likely, any chloromethyl compound **25a** (X = Cl) that had formed might have undergone oxidation by methyl sulfoxide [12] to give **28a**, which is the same as **29a**. It will be noted, however, that these products differ when R ≠ H, so it is possible to differentiate between the two pathways by starting with a 3'-substituted version of **23**. We prepared for this purpose the 3'-deuterio derivative **23b**. This compound was obtained by careful treatment of **15a** with potassium carbonate in methyl sulfoxide-d_6 containing deuterium oxide, followed by peracid oxidation of the resulting **15b** [13]. Pyrolysis of **23b** in methyl sulfoxide and treatment with HCl then afforded material that, lacking the formyl resonance in the ^{1}H-nmr spectrum, is clearly **29b** and not **28b**. We conclude that **29a** is formed from a dihydro intermediate rather than from **25a**. Since methyl sulfoxide is known to oxidize tetramethylene sulfide to the sulfoxide [14], and since the dehydrogenation of dihydrothiophenes induced by iodosylbenzene is thought to proceed *via* sulfoxide intermediates [15], it is possible that the formation of **29** involves the sulfoxide derivative of **30**.

More highly substituted compounds such as aryl-2-butynylsulfoxides also undergo thermal rearrangements to give condensed thiophenes [11a,b], so extension of the reactions of Scheme 4 to varieties of **23** bearing more complex 3'-substituents would appear to be warranted.

EXPERIMENTAL

General Procedures.

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined at 89.61 MHz (proton) and 22.52 MHz (^{13}C) on a JEOL FX90Q spectrometer. A Varian VXR-500 spectrometer was used to determine the NOE difference spectra for **20**. Proton chemical shifts were measured relative to internal tetramethylsilane whereas ^{13}C chemical shifts were measured relative to the solvent peak and then converted to the TMS scale. First order values are given for coupling constants and chemical shifts. Proton-carbon coupling constants were observed under gated decoupling conditions using an increased number of data points and a decreased spectral width to improve the digital resolution. Ultraviolet spectra were recorded on a Gilford Response II spectrophotometer. The tlc analyses were carried out with Analtech silica gel GF plates (250 μm), and separated materials were visualized with uv light and/or by spraying with 10% ethanolic sulfuric acid followed by heating. Preparative tlc separations were carried out on 1000 μm (20 x 20 cm) plates using 1:1 ethyl acetate-hexane, v/v, as the developing solvent. All evaporations were carried out under reduced pressure in a rotary evaporator, except for methyl sulfoxide, which was evaporated in a glass lyophilizer apparatus (Ace Glass, # 9547-10) using an oil vacuum pump, 2-propanol/dry ice in the condenser well, and a bath temperature of ~45°. Micro-analyses were performed by MHW Laboratories, Phoenix, Arizona.

1,3-Dimethyl-5-(2-butynyloxy)uracil (7).

Dry methyl sulfoxide (4 ml) was added to sodium hydride (618 mg of 60% oil-dispersion, 15.45 mmoles) that had been washed under nitrogen with dry tetrahydrofuran. A solution of **6** (1.00 g, 5.15 mmoles) [3] in dry methyl sulfoxide (5 ml) was added under nitrogen, and methyl iodide (6 ml, 0.096 mole) was added dropwise over a 30 minute period. After 2 hours stirring at room temperature under nitrogen, the solids were removed by filtration and washed with a small portion of dichloromethane. The filtrate and washings were diluted to 150 ml with dichloromethane and then washed with water (3 x 100 ml). The organic layer was dried (sodium sulfate), filtered and evaporated to dryness to afford a yellow residue (910 mg). Crystallization of this material from 20 ml of hot water gave 650 mg (61%) of pure **7**, mp 137-138°; uv (water): λ max 279 nm, λ min 246 nm; ^{1}H-nmr

(deuteriochloroform): δ 7.02 (1H, s, H-6), 4.64 (2H, q, H-1'a,b), 3.40 and 3.37 (two 3H s, 1-Me and 3-Me), 1.86 (3H, t, H-4'a,b,c), $^5J_{1',4'}$ = 2.4 Hz; ^{13}C nmr (methyl sulfoxide-d_6): δ 159.2 (C-4), 150.0 (C-2), 131.3 (C-5), 130.4 (C-6), 84.4 (C-3'), 74.2 (C-2'), 58.6 (C-1'), 36.2 (1-Me), 27.6 (3-Me), 3.1 (C-4'), $^1J_{C-6}$ = 181, $^1J_{C-1'}$ = 152, $^1J_{1-Me}$ = $^1J_{3-Me}$ = 142 [16], $^1J_{C-4'}$ = 132, $^2J_{C-2',H-1'}$ = 7.3, $^3J_{C-3',H-1'}$ = 3.7, $^2J_{C-3',H-4'}$ = 10.4, $^3J_{C-2',H-4'}$ = 4.3, $^3J_{C-6,1-CH_3}$ = $^3J_{1-CH_3,H-6}$ = 3.7 Hz.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.59; H, 5.72; N, 13.24.

1,3,6,7-Tetramethylfuro[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**11**).

A solution of **7** (100 mg, 0.48 mmole) in dimethylformamide (4 ml) was heated at 130-135° for 4 hours. Removal of solvent and crystallization of the residue from hot ethanol then afforded 55 mg (55%) of pure **11**, mp 191-192°; uv (water): λ max 282, sh 256 nm, λ min 238 nm; ^{1}H-nmr (deuteriochloroform): δ 3.64 (3H, s, 1-Me), 3.41 (3H, s, 3-Me), 2.36 (3H, q, C-6(7)Me), 2.24 (3H, q, C-7(6)Me), $^5J_{6-Me,7-Me}$ = 0.7 Hz [17]; ^{13}C-nmr (deuteriocholorform): δ 156.7 (C-6), 153.3 (C-4), 152.0 (C-2), 137.8 (C-7a), 129.1 (C-4a), 106.4 (C-7), 31.8 (1-Me), 28.2 (3-Me), 12.0 (6-Me), 10.0 (7-Me).

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.69; H, 5.72; N, 13.31.

1,3,8-Trimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**8**).

A solution of **7** (100 mg, 0.48 mmole) in dry methyl sulfoxide (5 ml) was heated at 130-135° for 2 hours. Removal of solvent afforded a dark brown residue that contained (tlc, ethyl acetate-hexane, 1:1 v/v) mostly **8**, small amounts of **11**, and traces of two less polar unidentified compounds. Preparative tlc, using double development, afforded 60 mg (60%) of **8** as a pale yellow solid that melted indistinctly over the range 100-110° dec; uv (water): λ max 336 nm, λ min 283 nm; ^{1}H-nmr (deuteriochloroform): δ 5.86 (1H, tq H-7), 4.48 (2H, dq H-6), 3.43 and 3.40 (two 3H s, *N*-methyls), 2.12 (3H, dt, 4-lines visible, 8-Me), $^5J_{6,Me}$ = $^4J_{7,Me}$ = 1.4 Hz [18], $J_{6,7}$ = 5.0 Hz; ^{13}C-nmr (deuteriochloroform): δ 158.0 (C-4), 151.2 (C-2), 135.0 (C-8a), 132.4 (C-4a), 127.1 (C-8), 123.4 (C-7), 64.3 (C-6), 36.6 (1-Me), 28.3 (3-Me), 19.2 (8-Me), $^1J_{C-7}$ = 167, $^1J_{C-6}$ = 149, $^1J_{8-Me}$ = 129, $^3J_{C-6,H-7}$ = 9.2, $^3J_{8-CH_3,H-7}$ = $^3J_{C-4a,H-6}$ = 6.1, $^3J_{C-4,3-CH_3}$ = 2.4 Hz.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.51; H, 5.96; N, 13.36.

1,3,7-Trimethylfuro[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**12**).

Sodium methoxide solution (0.56 ml of 25% w/v, 2.57 mmoles) was added to a solution of **6** (500 mg, 2.57 mmoles) in dry methyl sulfoxide (2 ml), and the mixture was heated at 70° for 2 hours. After cooling, solids were removed and washed with methanol, affording 260 mg (52%) of crystalline **12** with excellent tlc purity. This product crystallizes as needles from ethanol, mp 212-213°; uv (water): λ max 257 and 280 nm, λ min 235 and 265 nm; ^{1}H-nmr (deuteriochloroform): δ 7.44 (1H, q, H-6), 3.65 (3H, s, 1-Me), 3.42 (3H, s, 3-Me), 2.32 (3H, d, 7-Me), $^4J_{6,7-Me}$ = 1.1 Hz; ^{13}C-nmr (deuteriochloroform): δ 153.6 (C-4), 151.9 (C-2), 146.6 (C-6), 136.7 (C-7a), 131.6 (C-4a), 111.6 (C-7), 32.0 (1-Me), 28.3 (3-Me), 9.9 (7-Me), $^1J_{C-6}$ = 204, $^1J_{7-Me}$ = 129 Hz, $^3J_{C-6,7-CH_3}$ = 6.1, $^3J_{7-CH_3,H-6}$ = 1.2 Hz [19].

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.81; H, 5.03; N, 14.29.

Base-catalyzed Isomerization of 1,3-Dimethyl-5-(2-propynyloxy)-uracil (**6**) to Allene **9** with Sodium Hydroxide.

Sodium hydroxide (0.1 ml of 1*N* solution) was added to a suspension of **6** (125 mg) in methyl sulfoxide (1 ml). The reaction mixture, which darkens considerably, was stirred at room temperature for 18 hours, with occasional sonication to break up the larger particles. The reaction mixture was neutralized with hydrochloric acid and then diluted with 4 ml of water. Cooling induced crystallization of unchanged **6** (70 mg). The filtrate was evaporated to dryness, dichloromethane was added to the residue, and sodium chloride was removed by filtration. Removal of solvent then afforded an approximately 3:1 mixture of **6** and a second component that is probably the allene **9** (R = H). The ^{1}H-nmr spectrum of the mixture shows the resonances of **6** and additional signals at δ 7.20 (s), 6.87 (t) and 5.46 (d, J = 6.0 Hz) consistent with H-6, H-1' and H-3'a,b, respectively, of allene **9** (R = H). Attempts to separate these products by tlc in a wide variety of solvent combinations were not successful.

5-Chlorosulfonyl-1,3-dimethyluracil (**14**).

Chlorosulfonic acid (100 ml) was added cautiously to 1,3-dimethyluracil (20 g) [20] in a 500 ml round bottom flask. The solid quickly dissolves and the temperature of the solution, which rapidly approaches 100°, was controlled by intermittent cooling in an ice bath. After the initial reaction had subsided, the mixture was heated to reflux temperature for one hour. The cooled reaction mixture was transferred to a glass separatory funnel and then carefully added dropwise to a 2 ℓ beaker filled with crushed ice. When the ice had melted, the white solid was collected and washed with two 100 ml portions of cold water. This material (23 g, 65%), mp ~225° (decomposition, with shrinkage and darkening above 200°), analyzed as a hemihydrate after drying in air and was used in the next step without further purification.

Anal. Calcd. for $C_6H_7ClN_2O_4S{\cdot}0.5H_2O$: C, 29.10; H, 3.26; Cl, 14.32; N, 11.31; S, 12.95. Found: C, 28.97; H, 3.29; Cl, 14.41; N, 11.49; S, 12.76.

1,3-Dimethyl-5-(2-propynylthio)uracil (**15**).

A 10.0 g portion of the sulfonyl chloride **14** (40.4 mmoles) was suspended in water (80 ml), concentrated sulfuric acid (20 ml) was added, and the magnetically-stirred mixture was cooled in an ice-bath. Zinc dust (30 g) was added in portions over a ten minute period: foaming was controlled by occasional additions of ethyl acetate and by using a 1 liter beaker as the reaction vassel. Stirring was continued for 30 minutes at 0° and for another 30 minutes after the removal of the ice bath. An additional 5 g portion of zinc dust was added and the mixture was heated to near boiling on a steam bath. After 30 minutes of heating, the mixture was again cooled in ice and the resulting grey sludge, which contains the zinc salt of 1,3-dimethyl-5-thiouracil, was collected by filtration. The washed filter pad and paper were suspended in 1*N* sodium hydroxide (100 ml) under nitrogen and stirred vigorously while propargyl bromide (10 ml) was added. After 30 minutes at room temperature, the mixture was filtered, the filtrate was extracted with ethyl acetate (2 x 100 ml), and the organic layer was dried with sodium sulfate. Removal of solvent then afforded a syrup that crystallized readily from hot ethanol to afford 3.2 g (38%) of **15**, mp 124-125°; uv (water): λ max 280 nm, λ min 248 nm; ^{1}H-nmr (deuteriochloroform): δ 7.65 (1H, s, H-6), 3.50 (2H, d, H-1'a,b), 3.44 and 3.37 (two 3H s, 1-Me and 3-Me), 2.20 (1H, t, H-3'), $^4J_{1',3'}$ = 2.75 Hz; ^{13}C-nmr (methyl sulfoxide-d_6): δ 161.3 (C-4), 151.0 (C-2), 148.1 (C-6), 102.6 (C-5), 79.8 (C-2'), 74.5 (C-3'),

36.4 (1-Me), 27.9 (3-Me), 20.7 (C-1'), $^1J_{C-3'}$ = 251.7, $^1J_{C-6}$ = 185, $^1J_{C-1'}$ = 147, $^2J_{C-2',H-3'}$ = 50.3, $^3J_{C-2',H-1'}$ = 8.5, $^3J_{C-3',H-1'}$ = 4.3, $^3J_{C-1',H-3'}$ = 3.7, $^3J_{C-5,H-1'}$ = 4.1, $^3J_{C4,H-6}$ = 8.9, $^3J_{C-4,3-CH_3}$ = 2.4, $^3J_{C-6,1-CH_3}$ = 3.4, $^3J_{1-CH_3,H-6}$ = 3.7 Hz.

Anal. Calcd. for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32; S, 15.25. Found: C, 51.43; H, 4.95; N, 13.31; S, 15.07.

Base-catalyzed Isomerizations of 1,3-Dimethyl-5-(2-propynylthio)-uracil (**15**) to **19** and **22** with Sodium Hydride.

A solution of **15** (500 mg, 2.38 mmoles) in dry tetrahydrofuran (5 ml) containing methyl sulfoxide (0.1 ml) was added slowly under a nitrogen atmosphere to sodium hydride (114 mg, 2.85 mmoles of 60% oil-dispersion) that had been washed with tetrahydrofuran and decanted. The mixture was stirred at 40° for 2 hours and then evaporated to dryness. The dark residue was partitioned between brine (50 ml) and dichloromethane (50 ml), the organic layer was washed with brine and then dried over sodium sulfate. After filtration, concentration afforded 250 mg of a solid that was composed (nmr) of a 2:1 mixture of **19** and **22**. These products were separated by preparative tlc using triple development. Extraction of the major band (Rf 0.52) afforded 120 mg (24%) of 1,3-dimethyl-5-(1,2-propadienylthio)uracil (**19**), mp 110-112°; uv (water): λ max 269 nm, sh 300 nm, λ min 248 nm; ^{1}H-nmr (deuteriochloroform): δ 7.55 (1H, s, H-6), 5.84 (1H, t, H-1'), 4.95 (2H, d, H-3'), $^4J_{1',3'}$ = 6.2 Hz; ^{13}C-nmr (deuteriochloroform): δ 207.2 (C-2'), 161.5 (C-4), 151.4 (C-2), 146.1 (C-6), 105.6 (C-5), 86.3 (C-1'), 80.0 (C-3'), 37.1 (1-Me), 28.5 (3-Me), $^1J_{C-1'} \approx$ 189 [21], $^1J_{C-3'} \approx$ 170, $^1J_{C-6}$ = 182, $^3J_{C-6,1-CH_3}$ = 3.4, $^3J_{1-CH_3,H-6}$ = 3.7, $^3J_{C-4,H-6}$ = 8.9, $^3J_{C-4,3-CH_3}$ = 2.4 Hz.

Anal. Calcd. for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32; S, 15.25. Found: C, 51.21; H, 4.88; N, 13.15; S, 15.09.

Extraction of the minor band (Rf 0.49) afforded 63 mg (13%) of 1,3-dimethyl-5-(1-propynylthio)uracil (**22**), mp 110-111°; uv (water): λ max 280 nm, λ min 248 nm; ^{1}H-nmr (deuteriochloroform): δ 7.36 (1H, s, H-6), 3.47 (3H, s, 1-Me), 3.37 (3H, s, 3-Me), 2.06 (3H, s, H-3'a,b,c); ^{13}C-nmr (deuteriochloroform): δ 160.5 (C-4), 151.1 (C-2), 139.1 (C-6), 106.7 (C-5), 95.6 (C-2'), 62.8 (C-1'), 37.3 (1-Me), 28.3 (3-Me), 5.2 (C-3'), $^1J_{C-3'}$ = 132, $^1J_{C-6}$ = 182, $^2J_{C-2',H-3'}$ = 10.6, $^3J_{C-1',H-3'}$ = 4.9, $^3J_{C-4,H-6}$ = 8.6, $^3J_{C-4,3-CH_3}$ = 3.0, $^3J_{C-6,1-CH_3}$ = $^3J_{1-CH_3,H-6}$ = 3.7 Hz.

Anal. Calcd. for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32. Found: C, 51.51; H, 4.87; N, 13.17.

Base-catalyzed Isomerization of 1,3-Dimethyl-5-(2-propynylthio)-uracil (**15**) to Allene **19** with Sodium Hydroxide.

A 210 mg portion of **15** (1 mmole) was suspended in water (7 ml) and 1 ml of 1*N* sodium hydroxide (1 mmole) was added. The mixture was heated on a steam bath until solution occured (~5 minutes). After cooling, the solution was acidified with acetic acid to *p*H ~6, whereupon the allene **19** crystallized as colorless needles. After further cooling, 164 mg (78%) of material was obtained with physical properties (mp, nmr, tlc) identical with those of **19** prepared as above.

1,3,6-Trimethylthieno[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)dione (**17**) and 7-(Thiomethoxymethyl)-1,3,6-trimethylthieno[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**20a**).

A solution of **15** (400 mg) in methyl sulfoxide (3 ml) was heated at 145-147° for 12 hours. An inert atmosphere was maintained by connecting a nitrogen-filled balloon *via* a hypodermic needle and serum cap to the reaction vessel. The dark yellow reaction mixture was evaporated to dryness to afford a residue that contained (tlc) essentially two products. These were separated by preparative tlc using four plates. Extraction of the slower moving (major) band with ethyl acetate and crystallization of the residue from ethanol afforded 200 mg (50%) of **17**, mp 203-205°; uv (water): λ max 274 nm, large shoulder at 300 nm, λ min 248 nm; ^{1}H-nmr (deuteriochloroform): δ 6.66 (1H, q, H-7), 3.54 (3H, s, 1-Me), 3.42 (3H, s, 3-Me), 2.58 (3H, d, 6-Me), $^4J_{7,6-Me}$ = 1 Hz; ^{13}C-nmr (deuteriochloroform): δ 157.9 (C-4), 152.0 (C-2), 150.6 (C-6), 145.8 (C-7a), 114.5 (C-7), 110.6 (C-4a), 32.8 (1-Me), 28.2 (3-Me), 16.6 (6-Me), $^1J_{C-7}$ = 170, $^1J_{6-Me}$ = 130, $^3J_{C-7,6-CH_3}$ = 5.1, $^3J_{6-CH_3,H-7}$ = 3.4 Hz.

Anal. Calcd. for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32; S, 15.25. Found: C, 51.44; H. 4.97; N, 13.36; S, 15.01.

Extraction of the faster moving band with ethyl acetate and crystallization of the residue from ethanol afforded 91 mg (18%) of the thiomethyloxymethyl compound **20a**, mp 169-171°; uv (water): λ max 283 nm, sh 306 nm, λ min 250 nm; ^{1}H-nmr (deuteriochloroform): δ 3.94 (3H, s, 1-Me), 3.83 (2H, s, CH_2), 3.42 (3H, s, 3-Me), 2.53 (3H, s, C-6 Me), 2.13 (3H, s, SMe); ^{13}C-nmr (deuteriochloroform): δ 157.6 (C-4), 152.5 (C-2), 147.2 (C-6), 143.8 (C-7a), 123.1 (C-7), 111.2 (C-4a), 32.0 (1-Me), 30.8 (CH_2), 28.3 (3-Me), 15.6 (SMe), 15.1 (6-Me), $^1J_{CH_2}$ = 141, $^1J_{SMe}$ = 139 $^1J_{6-Me}$ = 130, $^3J_{CH_2,SCH_3}$ = 4.9, $^3J_{SCH_3,CH_2}$ = 2.4 Hz.

Anal. Calcd. for $C_{11}H_{14}N_2O_2S_2$: C, 48.87; H, 5.22; N, 10.36; S, 23.72. Found: C, 48.66; H, 5.50; N, 10.39; S, 23.49.

The deuterated compound **20b** was obtained along with **16** when the above reaction was conducted in methyl sulfoxide-d_6.

1,3-Dimethyl-5-(2-propynylthio)uracil-3'-d (**15b**).

A 100 mg portion of **15a** was dissolved in methyl sulfoxide-d_6 (1.5 ml) in a 5 mm nmr tube. Deuterium oxide (0.2 ml, 100%) and finely powdered potassium carbonate (5 mg) were added, and the tube contents were mixed by inversion and brief sonication. Nmr monitoring of the reaction showed that the exchange of H-3' for deuterium was complete within 5 minutes. The reaction mixture was acidified with acetic acid and solvents were removed. Crystallization of the residue from ethanol afforded 60 mg of **15b** as fine needles. An additional 20 mg of product (80% total) was obtained by subjecting the residue obtained on evaporation of the mother liquor to preparative tlc. The appearance of the H-1' signal as a two-proton singlet in the ^{1}H-nmr spectrum of isolated **15b** confirms that deuteration is restricted to the C-3' position under these conditions.

1,3-Dimethyl-5-(2-propynylsulfinyl)uracil (**23a**).

A 1.00 g sample of **15** (4.76 mmoles) was dissolved in a mixture of ethanol (40 ml) and dichloromethane (5 ml), and the stirred solution was cooled in an ice bath. A solution of 3-chloroperoxybenzoic acid (1.03 g, 80% technical grade, 4.76 mmoles) in ethanol (10 ml) was added dropwise over a 30 minute period. Stirring was continued for an additional 30 minutes before the solids were collected and washed with cold ethanol. The white crystalline product (990 mg) obtained after drying was recrystallized from ethyl acetate to afford 800 mg (74%) of **23**, mp 146-148°; ^{1}H-nmr (methyl sulfoxide-d_6): δ 7.98 (1H, s, H-6), 3.96 (2H, dq, H-1'ab), 3.45 (3H, s, NMe), 3.39 (1H, t, H-3'), 3.18 (3H, s, NMe), $J_{1'a,1'b}$ = 16.5 Hz, $J_{1',3'}$ = 2.75, Hz; ^{13}C-nmr (methyl sulfoxide-d_6): δ 159.0 (C-4), 151.0 (C-2), 145.3 (C-6), 112.0 (C-5), 78.7 (C-3'), 73.9 (C-2'), 42.9 (C-1'), 33.2 (1-Me), 27.4 (3-Me), $^1J_{C-3}$ =

252.7, $^1J_{C\text{-}6}$ = 185.5, $^1J_{C\text{-}1'}$ = 147.1, $^2J_{C\text{-}2',H\text{-}3'}$ = 51.3, $^3J_{C\text{-}2',H\text{-}1'}$ = 9.2, $^3J_{C\text{-}3',H\text{-}1'}$ = 4.3, $^3J_{C\text{-}1',H\text{-}3'}$ = $^3J_{C\text{-}6,1\text{-}CH_3}$ = $^3J_{1\text{-}CH_3,H\text{-}6}$ = 3.7 Hz.

Anal. Calcd. for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.46; N, 12.38; S, 14.17. Found: C, 48.01; H, 4.42; N, 12.31; S, 14.36.

1,3-Dimethyl-5-(2-propynylsulfinyl)uracil-3'-d (**23b**).

This material was prepared from **15b** using the procedure described above for **23a**. As expected, the absence of H-3' in **23b** causes the H-1' signal to appear as a quartet rather that a double quartet in the ^{1}H-nmr spectrum.

1,3-Dimethyl-7-formylthieno[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**29a**).

A solution of **23a** (300 mg, 1.33 mmoles) in methyl sulfoxide (5 ml) was heated at 105-107° for 90 minutes. Concentrated hydrochloric acid (0.2 ml) was added and heating was continued for another 5 minutes. The cooled solution was evaporated to dryness and the residue was dissolved in hot ethanol. Cooling induced crystallization of **29a**, which was obtained in the form of slightly discolored needles (140 mg, 47%) that nevertheless migrated as a single spot on tlc in ethyl acetate. Colorless material obtained by recrystallization from aqueous ethanol showed the following properties, mp 238-240°; uv (90% aqueous methanol): λ max 309, 237, sh 215 nm, λ min 286 nm, 237/309 = 4.44; ^{1}H-nmr (deuteriochloroform): δ 10.10 (1H, s, C*H*O), 8.51 (1H, s, H-6), 3.84 (3H, s, 1-Me), 3.47 (3H, s, 3-Me); ^{13}C-nmr (deuteriochloroform): δ 182.6 (CHO), 157.9 (C-4), 152.1 (C-2), 145.6 (C-6), 143.0 (C-7a), 133.1 (C-7), 116.5 (C-4a), 36.7 (1-Me), 28.6 (3-Me), $^1J_{CHO}$ = 182.5, $^1J_{C\text{-}6}$ = 187.4, $^3J_{CHO,H\text{-}6}$ = 3.7, $^3J_{C\text{-}6,CHO}$ = 2.4 Hz.

Anal. Calcd. for $C_9H_8N_2O_3S$: C, 48.21; H, 3.60; N, 12.49; S, 14.30. Found: C, 48.36; H, 3.85; N, 12.41; S, 14.35.

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[19] For comparison, the 6-methyl isomer **3** (R = H) shows the following ^{13}C-nmr spectrum in deuteriochloroform: δ 160.5 (C-6), 152.9 (C-4), 151.5 (C-2), 139.4 (C-7a), 129.0 (C-4a), 97.6 (C-7), 32.3 (1-Me), 27.9 (3-Me), 14.2 (6-Me), $^1J_{C\text{-}7}$ = 180, $^1J_{6\text{-}Me}$ = 130, $^3J_{C\text{-}7,6\text{-}CH_3}$ = 3.4, $^3J_{6\text{-}CH_3,H\text{-}7}$ = 1 Hz.

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