Sulfur Migration in Reactions of *S*-(β-D-Ribofuranosyl)-5-mercaptouracil Derivatives (1)

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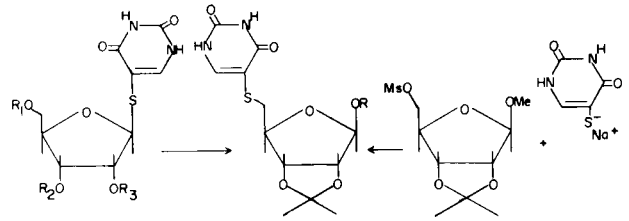
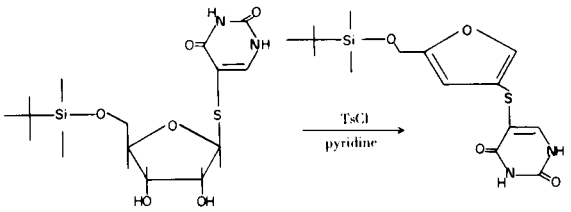
Although there are numerous anhydronucleosides in which sulfur joins a purine (2) or pyrimidine (3) base to a carbohydrate moiety, only one anhydronucleoside, 3,4,6 tri-*O*-acetyl-D-mannopyrano[*cis*-1,2-*b*]dihydrobenzothiazine (4), involves a sulfur linkage to C-1′ of the carbohydrate moiety. We report here several rearrangements involving sulfur migration observed during unsuccessful attempts to utilize *S*-(β-D-ribofuranosyl)-5-mercaptouracil (**1**) (5) or related compounds as intermediates for the synthesis of such *C*-1′-S-anhydronucleosides, which are preferred starting materials for a proposed (1a) silver ion catalyzed sulfur extrusion reaction leading to *C*-nucleosides.

In an attempt to form a linkage between O-4 of the pyrimidine moiety and C-5′ of the carbohydrate moiety, *S*-(2′,3′-*O*-isopropylidene-5′-*O*-*p*-toluenesulfonyl-β-D-ribofuranosyl)-5-mercaptouracil (**2**), derived from **1** using standard methods (6), was treated with sodium bicarbonate in refluxing dimethylformamide (7). The only product isolated was the 5′-*S*-uracilylriboside **3**, produced *via* sulfur migration. The structure of **3** was deduced by examination of its mass and pmr spectra. Particularly



1 R_1 R_2 R_3 = H
2 R_1 R_3 $C(CH_3)_2$
R_2 $SO_2C_6H_4CH_3$ (*p*)
3 R = H
4 R = CH_3
5
6

indicative of structure **3** was the shift of the pmr signal for the carbohydrate C-5′ protons from δ 4.23 to δ 2.81 which established the point of attachment of the sulfur atom and the 1′-H singlet at δ 5.18 corresponding to the β-configuration for the ribofuranoside (8). The remainder of the pmr spectrum is similar to those observed for other "reversed" nucleosides (8,9). The rearrangement product was established conclusively as **3** by conversion to the corresponding methyl riboside **4** which was also prepared



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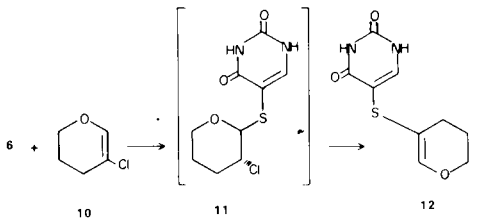
independently by treatment of methyl 2,3-*O*-isopropylidene-5-*O*-methanesulfonyl-β-D-ribofuranoside (**5**) (10) with the sodium derivative of 5-mercaptouracil (**6**) (11).

Migration of sulfur from C-1′ to C-2′ of the ribofuranosyl moiety occurred when the 5′-blocked nucleoside **7**, prepared by treatment of **1** with *t*-butyldimethylsilyl chloride (12), was treated with *p*-toluenesulfonyl chloride in pyridine. Under usual conditions (room temperature (13)) no reaction occurred; when the reaction mixture was warmed to 60-70° the reaction proceeded yielding the rearranged furan **8**, presumably *via* the intermediacy of the 2′-*p*-toluenesulfonate (14).

The structure of furan **8** was apparent following examination of its mass and pmr spectra. Comparison of the pmr spectrum of **8** with that reported (14) for 5-(benzoyloxymethyl)-2-*S*-benzylfuran-2-thiol (**9**) shows many similarities. The signal for the 4-furanyl proton of **8** appears at δ 6.40 and that for **9** at δ 6.35; the 2-furanyl proton for **8** accurs at δ 7.58 and the corresponding proton for **9** is seen at δ 7.49. The 6-uracil proton appears at δ 7.70. In the mass spectrum of **8**, no molecular ion is evident; the ion at highest mass, produced by loss of a methyl radical, appears at *m/e* 339. The base peak, *m/e* 297, corresponds to loss of a *t*-butyl group. The ion observed at *m/e* 223, resulting from loss of the 5′-*t*-butyldimethylsilyloxy group, is an indication of the benzylic nature of its attachment (13).

An apparently similar reaction sequence occurred upon treatment of 5-mercaptouracil (**6**) (11) with 5-chloro-3,4 dihydro-2*H*-pyran (**10**) (15). The expected product **11** was not isolated; rather, under the reaction conditions, **11** lost the elements of hydrogen chloride with concurrent sulfur migration to produce *S*-[5′-(3′,4′-dihydro-2′*H*-pyranly)]-5-mercaptouracil (**12**).



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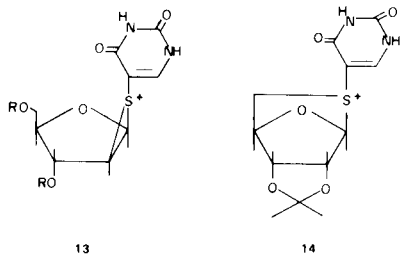
The 1,2-sulfur migration reactions are envisaged as proceeding through nucleophilic attack by sulfur on the adjacent electron deficient carbon to produce an intermediate episulfonium ion (**13**) (14, 16) followed by subsequent elimination to the observed products. The 1,5-sulfur migration appears to involve an analogous cyclic sulfonium ion (**14**) which, because of the adjacent oxygen is opened exclusively at C-1′. The absence of water or other solvent nucleophile in the reaction medium used for the conversion **2** → **3** indicates that the 1′-*p*-toluene sulfonate formed in a transposition reaction (16) is probably the initial product. Hydrolysis of this intermediate produces exclusively the β-glycoside **3.**



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EXPERIMENTAL (17)

S-(2′,3′-*O*-Isopropylidene-β-D-ribofuranosyl)-5-mercaptouracil (**15**).

To a stirred slurry of 1.15 g. (4.26 mmoles) of *S*-(β-D-ribofuranosyl)-5-mercaptouracil (**1**) (5) in 100 ml. of acetone was added 7 ml. of 2,2 dimethoxypropane and 500 mg. of *p*-toluenesulfonic acid monohydrate. After stirring at room temperature for 18 hours, the reaction mixture was evaporated to dryness and ether was added to give, upon filtration, 1.22 g. of crude **15**. Recrystallization from ethanol gave 1.16 g. (88%) of **15**, m.p. 270-272°: nmr (DMSO-d_6): δ 7.8 (s, C-6 H), 5.35 (s, C-1′H), 4.73 (s, C-2′, C-3′H's), 4.12 (m, C-4′H), 3.54 (m, C-5′H's); 1.38, 1.27 (s's, isopropyl); uv (*p*H 2): λ max 284 nm.

Anal. Calcd. for $C_{12}H_{16}N_2O_6S$: C, 45.2; H, 5.10; N, 8.96. Found: C, 45.4; H, 5.11; N, 8.82.

S-(2,3-*O*-Isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranosyl)-5-mercaptouracil (**2**).

To a solution of 931 mg. (2.95 mmoles) of **15** in 25 ml. of dry pyridine at 0° was added, with stirring, 835 mg. (4.38 mmoles) of recrystallized *p*-toluenesulfonyl chloride. The reaction mixture was allowed to stand at 4° for 36 hours, then 2 ml. of water was added and the solution was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate.. The ethyl acetate solution was washed with water, dried over sodium sulfate and evaporated to an oil. The oil was recrystallized from acetone-methanol-hexane to give 973 mg. (70%) of **2**, m.p. 107-110°. An analytical sample obtained by a second recrystallization using the same solvent system exhibited: m.p. 110-111.5°; nmr (DMSO-d_6): δ 7.83, 7.49 (4, AB quartet, J = 7 Hz, aromatic), 7.56 (s, C-6H), 5.44 (s, C-1′H), 4.71 (s, C-2′, C-3′ H's), 4.23 (s, 3, C-4, C-5 H's), 2.42 (s, CH_3-Ar), 1.37, 1.24 (s's, isopropyl); uv (*p*H 13): λ max 223, 295 nm.

Anal. Calcd. for $C_{19}H_{22}N_2O_8S_2$: C, 48.5; H, 4.71; N, 5.95. Found: C, 48.5; H, 4.92; N, 5.74.

S-[5′-(2′,3′-*O*-Isopropylidene)-β-D-ribofuranosyl]-5-mercaptouracil (**3**).

A solution of 600 mg. (1.28 mmoles) of tosylate **2** and 150 mg. of sodium bicarbonate in 20 ml. of dry dimethylformamide was immersed in an oil bath at 120° ± 5° for 15 minutes. The reaction mixture was cooled and the solvent was removed under reduced pressure. The residue was triturated with acetone and filtered to yield 242 mg. (93%) of sodium *p*-toluene sulfonate. The acetone filtrate was removed to yield a crude product which could not be induced to crystallize. It was carried on to the next step without further purification. A sample of **3** purified by colum chromatography exhibited nmr (DMSO-d_6): 7.57 (s, C-6H), 5.18 (s, C-1′H), 4.69, 4.46 (d of d, J = 6 Hz, C-2′, C-3′ H's). 3.96 (d of d, J = 6 Hz, 3 Hz, C-4′H), 2.81 (m, C-5′H's), 1.33, 1.21 (s's, isopropyl).

S-[Methyl 5′-(2′,3′-*O*-isopropylidene)-β-D-ribofuranosyl]-5-mercaptouracil (**4**).

A. (8)

To a solution of 2.55 g. (17.1 mmoles) of 5-mercaptouracil (**6**) (11) in 200 ml. of dry dimethylformamide, under nitrogen, was added 810 mg. (17.7 mmoles) of a 53% dispersion of sodium hydride in mineral oil.

After 10 minutes, 0.5 g. of sodium iodide and 5.0 g. (17.7 mmoles) of methyl 2,3-*O*-isopropylidene-5-*O*-methanesulfonyl-ribose (**5**) (10) was added and the solution was heated under reflux for 30 minutes. The solvent was removed under reduced pressure and the residue was dissolved in 250 ml. of ethyl acetate; the ethyl acetate solution was filtered from a small amount of 5-uracilyl disulfide (11), washed with water, dried over sodium sulfate and evaporated to an oil which was placed on a short column of silica gel. Elution with chloroform removed unreacted and polymeric carbohydrate products. Elution with ethyl acetate yielded an oil which on trituration with hot ethyl acetate produced 1.50 g. (15.6%) of **4**, m.p. 227-230°. An analytical sample obtained from ethanol exhibited m.p. 229-231°; nmr (DMSO-d_6): δ 7.63 (s, C-6 H) 4.90 (s, C-1′ H) 4.73, 4.59 (d of d, J = 6 Hz, C-2′, C-3′ H's), 4.08 (m, C-4′ H), 2.76 (m, C-5′ H's), 1.36, 1.25 s's, isopropyl).

Anal. Calcd. for $C_{13}H_{18}N_2O_6S$: C, 47.3; H, 5.49; N, 8.48. Found: C, 47.4; H, 5.54; N, 8.45.

B.

A mixture of crude **3** (prepared from 600 mg. of **2**), 30 ml. of acetone, 3 ml. of dimethoxypropane and 20 ml. of methanol containing 2 ml. of methanol saturated with hydrogen chloride at 0° was stirred overnight at room temperature. Three ml. of pyridine was added and the solution was evaporated to an oil. The oil was crystallized from ethanol to give 156 mg. (38%) of **4**, m.p. 228-230°, mixed m.p. 228-230°.

S-[5′-*O*-(*t*-Butyldimethylsilyl)-β-D-ribofuranosyl]-5-mercaptouracil (**7**) (13).

To 9 ml. of anhydrous dimethylformamide was added 2.37 g.

(9.31 mmoles) of *S*-(β-D-ribofuranosyl)-5-mercaptouracil (**1**) (5), 1.46 g. (23.3 mmoles) of imidazole and 1.42 g. (10.2 mmoles) of *t*-butyldimethylchlorosilane (12). The mixture was tightly stoppered and left 48 hours at room temperature. The solution was then diluted with 110 ml. of methylene chloride and the resulting cloudy suspension was stored at 0° overnight. After filtration, there was realized 3.5 g. of a semi-crystalline solid. The crude product in ethyl acetate was heated under reflux and separated by filtration. This process was repeated until no further material was extracted. The ethyl acetate solution was filtered through a short column of silica gel and concentrated to a small volume providing 1.47 g. (44%) of *S*-[5′-*O*-(*t*-butyldimethylsilyl)-β-D-ribofuranosyl]-5-mercaptouracil (**7**) as colorless crystals, m.p. 210-213°.

Anal. Calcd. for $C_{15}H_{26}N_2O_6SSi$: C, 46.1; H, 6.71; N, 7.17. Found: C, 46.2; H, 7.02; N, 7.28.

Reaction of *S*-[5′-*O*-(*t*-Butyldimethylsilyl)-β-D-ribofuranosyl]-5-mercaptouracil (**7**) with *p*-Toluenesulfonyl Chloride.

To 15 ml. of dry pyridine was added 300 mg. of **7** and 149 mg. (1.02 equivalents) of *p*-toluenesulfonyl chloride. The solution was heated (60-70°) for 3 hours and then poured into ice water. The mixture was extracted with ethyl acetate: the combined ethyl acetate extracts were washed with a dilute solution of copper sulfate, and water, dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel plates with ether as eluent. The product appeared as a blue fluorescent band at Rf. 0.6. After extraction from the silica gel and evaporation of the solvent a minor yellow impurity was removed by trituration with ethyl acetate leaving 8 mg. (3%) of **8** as a colorless powder, m.p. 240-243° dec.; nmr (DMSO-d_6): δ 7.70 (s, C-6 H), 7.58 (s, C-2′ H), 6.40 (s, C-4′ H), 4.57 (s, 2, CH_2), 0.82 ppm (s, *t*-butyl H's); mass spectrum, *m/e* (rel intensity): 339 (3), 297 (100), 279 (7), 251 (5), 223 (20), 180 (10), 169 (5), 153 (13), 143 (4), 112 (3), 97 (6), 75 (21), 69 (24).

Anal. Calcd. for $C_{15}H_{22}N_2O_4SSi$: C, 50.8; H, 6.25; N, 7.90. Found: C, 51.0; H, 6.28; N, 8.03.

S-[5′-(3′,4′-Dihydro-2*H*-pyranyl)]-5-mercaptouracil (**12**).

A mixture of 0.72 g. (5.0 mmoles) of 5-mercaptouracil (**6**) (11) and 0.9 ml. (8.5 mmoles) of 5-chloro-3,4-dihydro-2*H*-pyran (**10**) (15) in 50 ml. of dioxane was heated under reflux for 12 hours. The solvent was removed *in vacuo* and the residue was triturated with 100 ml. of hot tetrahydrofuran and filtered. Evaporation of the filtrate yielded 0.68 g. (60%) of **12**, m.p. 248-252°; nmr (DMSO-d_6): δ 11.2 (br, NH), 7.45 (s, C-6H), 6.88 (s, C-2′ H), 3.98 (t, J = 5 Hz, C-6′ H's); 2.0 (m, C-4′, C-5′ H's); uv (pH 7.5): λ max 240 nm; (pH 12) λ max 240, 296 nm.

Anal. Calcd. for $C_9H_{10}N_2O_3S \cdot 1/2\ H_2O$: C, 46.0; H, 4.71; N, 11.9. Found: C, 46.1; H, 4.71; N, 12.2.

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