mixture of 15 g (0.18 mol) of cyclohexene and 40 g (0.4 mol) of TFE with stirring. After 15 min the solution is poured into water, neutralized with sodium hydrogen carbonate, and extracted with trichlorofluoromethane (3 × 10 mL). After drying of the mixture over sodium sulfate and distillation of the solvent and residue, 22 g (64%) of ether was obtained; bp 41–42 °C (13 mmHg). The volatile product, which still contained 6% olefin, was purified by distillation over a 1-m spinning-band column. Anal. Calcd for $C_8H_{13}OF_3$: C, 52.74; H, 7.19. Found: C, 52.80; H, 7.31.

Whereas reaction of TFE and acid with cholest-5-ene only led to rearranged olefins (^{13}C NMR), the same method was successful in the preparation of the following.

1-Methylcyclohexyl Trifluoroethyl Ether (4a), bp 44 °C (14 mmHg; after spinning-band distillation). Anal. Calcd for $C_9H_{15}OF_3$: C, 55.09; H, 7.71. Found: C, 55.10; H, 7.64.

Hexafluoroisopropyl ethers of cyclohexanol (53%) and 1-methylcyclohexanol (35%) were prepared only in small quantities for spectroscopic comparison.

Ether Cleavage Experiments. Treatment of cycloalkyl methyl and steroid methyl ethers with boron trifluoride and lithium iodide in acetic anhydride is known to yield acetates with retention of configuration.[20] This method was successfully tested with several primary ethers as well as with secondary and tertiary fluoroalkyl ethers: **5** gave 91% conversion, 89% acetate, and 6% olefin; **4a** gave 94% conversion, 90% acetate, and 10% olefin; **4b** gave 85% conversion, 95% acetate, and 5% olefin (GLC). No acetate, however, could be obtained from the steroid (**3**) solvolysis products.

Alternatively, a recently published reductive cleavage method[21] was modified as follows: 1 mmol of the ether was stirred under reflux with 1 mmol of lithium aluminium hydride and 10 mmol of boron trifluoride in diethyl ether. After cautious addition of water, GLC analysis of the ether solution showed only 10% conversion with **4a**, yielding 37% 1-methylcyclohexanol and 62% 1-methylcyclohexene.

Registry No. 1 (X = H), 5454-79-5; 1 (X = Ts), 37690-41-8; 2 (X = H), 21273-02-9; 2 (X = Ts), 957-27-7; 3 (X = H), 80-97-7; 3 (X = Ts), 3381-52-0; 3 (X = α-CH_2CF_3), 80764-76-7; 3 (X = β-$CH(CF_3)_2$), 80764-77-8; **4a**, 80764-78-9; **4b**, 80764-79-0; **5**, 80764-80-3; *cis*-3-methylcyclohexyl trifluoroethyl ether, 80764-81-4; *trans*-3-methylcyclohexyl trifluoroethyl ether, 80764-82-5; cyclohexyl hexafluoroisopropyl ether, 15233-00-8.

(20) H. Youssefyeh and Y. Mazur, *Tetrahedron Lett.* 1287 (1972).
(21) H. C. Brown and S. Krishnamurthy, *J. Org. Chem.*, **44**, 3678 (1979).

Simplified Synthesis of 5-Mercaptouracil Riboside Derivatives

F. J. Dinan,* J. Chodkowski, J. P. Barren, D. M. Robinson, and D. V. Reinhardt

Department of Chemistry, Canisius College, Buffalo, New York 14208

T. J. Bardos

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Amherst, New York 14260

Received October 2, 1981

The conventional preparation of nucleosides involves a rather lengthy synthetic procedure. In the case of one of the most preferred general methods the base to be used must generally be converted into a moisture-sensitive trimethylsilyl derivative. In some cases the catalyst used to effect formation of the nucleoside bond also requires trimethylsilylation. Condensation of the base with the sugar to be used normally takes place in yet another synthetic step. The need to distill, transfer, and otherwise handle these delicate materials introduces an element of difficulty into conventional nucleoside synthesis.

Generally, syntheses of this type utilize a blocked halo sugar. Because of the lack of long-term stability which characterizes them, sugars of this type are best freshly prepared shortly before the synthesis is undertaken.

A further area of difficulty which characterizes conventional nucleoside syntheses is the need to separate mixtures of the α and β anomers of the nucleoside which are normally formed in these reactions. Generally, separation of these isomers is effected by either fractional crystallization or chromatography. In either case, the separation procedure frequently proves costly in terms of both time and materials.

Recently, a simplified method for the preparation of pyrimidine and purine ribosides which either eliminates or greatly attenuates the difficulties which characterize the conventional synthetic procedures utilized in nucleoside syntheses has been reported.[1] This procedure involves the in situ formation of the silylated base and catalyst and their reaction with a stable, commercially available blocked ribose sugar to afford the product nucleoside in a single synthetic step. Furthermore, this method also results in formation of the desired β form of the synthetic riboside in a high state of purity, thereby eliminating the need for separation of the α isomer of the nucleoside.

Results and Discussion

The present study was undertaken to investigate the application of this method to the synthesis of a variety of ribosides which incorporate derivatives of 5-mercaptouracil as the base. This procedure has been found to be effective with a wide variety of substituents attached to the 5-sulfur atom.

Generally, the 5-S-alkylated derivatives of 5-mercaptouracil used in this study were prepared by treatment of the pyrimidine base with the desired alkylating agent under conditions which enhance sulfur alkylation while minimizing reaction at any of the several alternate sites at which alkylation could occur. The substantial difference in acidity between the sulfhydryl and hydroxyl groups of 5-mercaptouracil[2] allows for highly selective alkylation of the 5-sulfur atom.

The tendency for 5-mercaptouracil to undergo facile autoxidation to form the corresponding disulfide in basic solution has been reported.[3] Occurrence of this dimerization would prevent effective alkylation of the 5-sulfur atom of **1** and therefore must be prevented or minimized. The use of anhydrous methanol as the solvent for the alkylation reactions proved to be effective in both reducing the tendency of **1** to undergo dimerization and in allowing effective alkylation of the sulfur atom to occur. The only substituent which could not be introduced successfully via this general procedure was the vinyl group.

Pyrimidines having vinyl or vinylic groups in the 5-position often display substantial biological activity.[4] For this reason synthesis of an 5-*S*-vinyl derivative of **1** was deemed desirable. However, attempts to prepare this product via direct alkylation, dehydration of 5-[(2-hydroxyethyl)thio]uracil (**2**), and dehydrohalogenation of 5-(2-chloroethyl)thio]uracil (**3**) proved unsuccessful. A vinylic derivative of **1**, however, was prepared from the 5-*S*-allyl derivative **4** by isomerization of the allylic double

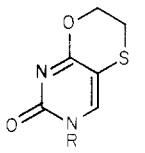
(1) H. Vorbruggen and B. Bennua, *Tetrahedron Lett.*, 1339 (1978).
(2) T. J. Bardos and T. I. Kalman, *J. Pharm. Sci.*, **55**, 606 (1966).
(3) T. I. Kalman and T. J. Bardos, *J. Am. Chem. Soc.*, **89**, 1171 (1967).
(4) Y. C. Cheng, B. A. Domin, R. A. Sharma, and M. Bobek, *Antimicrob. Agents Chemother.*, 10, 119 (1976).

0022-3263/82/1947-1769$01.25/0

bond. Treatment of **4** in refluxing Claisen's alkali[5] afforded the more thermodynamically stable 5-*S*-(methylvinyl) isomer **5** in 40% yield.

Identification of **5** as the isomerization product was confirmed by its ^{1}H NMR spectrum which indicated the presence of a vinylic protons as well as a methyl doublet (δ 1.73, J = 5.0 Hz). HPLC investigation of the isomerization reaction product on a C_{18} column by using an isocratic mixture of 10% methanol in water showed the presence of two peaks in a 2:1 area ratio which presumably correspond to the *E* and *Z* isomers of **5**. The smaller peak is assumed to be attributable to the less thermodynamically stable *Z* isomer.

Formation of the bicyclic oxathiin–pyrimidine derivative **9** was carried out in two steps analogous to those previously used for the formation of an oxetane–pyrimidine derivative.[6] Alkylation of **1** with 2-bromoethanol afforded the β-hydroxyethyl derivative **2**. Cyclic dehydration of **2** in anhydrous sulfuric acid afforded **9**. The ^{1}H NMR spectrum of **9** confirms its structure; it is characterized by a pair of triplet resonances at δ 4.6 and 3.1 (J = 5 Hz) corresponding to the A_2X_2 protons of the oxathiin ring.[7] The infrared spectrum of **9** which contains only one amide carbonyl absorption also supports the structure assignment.



9, R = H
16, R = 

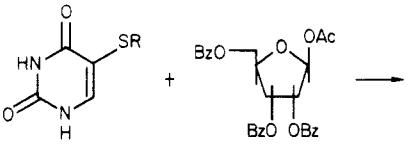
The catalyst used for the preparation of the nucleosides **11–15** is the trimethylsilyl ester of periflourobutanesulfonic acid. This material, which is formed in situ by the reaction of the potassium salt of this acid with trimethylsilyl chloride (Scheme I), was found to catalyze effectively the reaction between the 1-nitrogen atom of the various 5-S-alkylated pyrimidine rings and the peracylated riboside and ribose sugar (Scheme I). These reactions afford moderate to good yields of the pyrimidine ribosides. Total reaction times are of the order of 16–20 h, and workup procedures involve only simple extractions and crystallizations. Scheme I outlines the chemistry of the in situ nucleoside syntheses.

Each of the 5-S-alkylated ribosides formed in this study afforded a ^{1}H NMR spectrum consistent with that anticipated for the alkyl group attached to the sulfur atom. Infrared data, where applicable, also substantiated the presence of the appropriate functional groups.

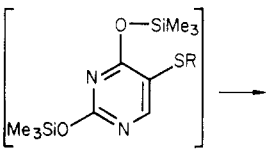
In all cases the nucleosides formed either exclusively or nearly so in the β-anomeric configuration as indicated by the ^{1}H NMR spectra of the blocked and deblocked nucleosides. This determination is based upon the appearance of the anomeric proton as a doublet at δ 5.9–6.3 having a J value of 5–6 Hz.[8] The ^{1}H NMR spectrum of the α anomer of the ribosides is characterized by a more deshielded anomeric proton resonance (δ 6.8) and a smaller coupling constant (J = 3–4 Hz). The ^{1}H NMR spectrum of the nucleosides formed in this study fail to display any resonance in the region characteristic of α-anomeric protons.

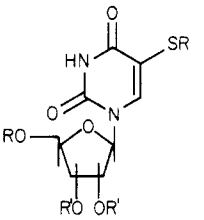
Scheme I

$$C_4F_9SO_3K + Me_3SiCl \longrightarrow Me_3SiSO_3C_4F_9 + KCl$$



1, R = H
2, R = CH_2CH_2OH
3, R = CH_2CH_2Cl
4, R = $CH_2CH{=}CH_2$
5, R = $CH{=}CHCH_3$
6, R = $CH_2C{\equiv}CH$
7, R = CH_3
8, R = $CH_2C_6H_5$





11, R = $CH_2CH{=}CH_2$; R′ = COC_6H_5
11a, R = $CH_2CH{=}CH_2$; R′ = H
12, R = $CH{=}CHCH_3$; R′ = COC_6H_5
12a, R = $CH{=}CHCH_3$; R′ = H
13, R = $CH_2C{\equiv}CH$; R′ = COC_6H_5
13a, R = $CH_2C{\equiv}CH$; R′ = H
14, R = CH_3; R′ = COC_6H_5
14a, R = CH_3; R′ = H
15, R = $CH_2C_6H_5$; R′ = COC_6H_5
15a, R = $CH_2C_6H_5$; R′ = H

Further evidence that these nucleosides are not significantly contaminated by the α anomer is provided by thin-layer chromatography. Investigation of the product nucleosides by using this technique with solvent systems which have previously been found to be effective for the separation of α- and β-riboside anomers[9] afforded only a single spot.

Investigation of the riboside **12**, prepared from the mixture of *Z* and *E* forms of the vinylic base **5**, by HPLC under conditions similar to those used for examination of **5** again disclosed two peaks in a 2:1 ratio. As before, these peaks are presumed to correspond to the *Z* and *E* isomers of the *S*-methylvinyl riboside **14**.

It should be noted that the *S*-propargyl riboside **15** is less stable than, for example, the homologous *S*-allyl and *S*-vinyl ribosides **13** and **14**. Whereas the latter compounds are stable for long periods in air, riboside **15** darkens when exposed to air for several hours, and the deblocked nucleoside darkens more rapidly upon exposure to air.

Whereas the blocked bicyclic riboside **16** could be formed from the base **9**, repeated attempts to deblock this nucleoside were unsuccessful.

Exclusive formation of the β anomer in each of the reactions carried out by using this in situ procedure could

(5) L. Fieser and M. Fieser. "Reagents for Organic Synthesis", Wiley, New York, 1967, 153.
(6) J. D. Fissekis and F. Sweet, *J. Org. Chem.*, **38**, 264 (1973).
(7) R. H. Bible "Interpretation of NMR Spectra", Plenum Press, New York, 1965, pp 97–102.
(8) L. B. Townsend, "Synthetic Procedures in Nucleic Acid Chemistry", Vol. 2, W. W. Zorbach and R. S. Tipson, Eds., Wiley-Interscience, New York, 1973, pp 267–298, and references therein.
(9) E. K. Ryu and T. J. Bardos, *J. Heterocycl. Chem.* **16**, 1049 (1979).

be accounted for by a mechanism which involves α-side participation of the 2-benzoyl group in the formation of an acyloxonium ion followed by attack of the pyrimidine base from the β side of the sugar. We are currently studying the HPLC and ^{13}C NMR spectra of peracylated sugar and catalyst mixtures in order to determine whether absorptions characteristic of the proposed acyloxonium ion are present.

Investigation of the pharmacological properties of the ribosides prepared in this study will be undertaken.

Experimental Section

Melting points were determined on a Mel-Temp apparatus (capillary method) and are unconnected. NMR spectra were determined on a Hitachi Perkin-Elmer R-24B spectrometer with Me_4Si as a reference standard. Infrared spectra were obtained by using a Beckman IR-4250 spectrometer. All solvents were dried by using standard procedures. Reagents were desiccated over P_2O_5 under vacuum prior to use, and reactions were run in a controlled-temperature and -humidity environment. Microanalyses were performed by Atlantic Microlabs, Inc.

5-(Allylthio)uracil (4) and 5-(propargylthio)uracil (6) were prepared by previously reported procedures.[10]

5-[(2-Hydroxyethyl)thio]uracil (2). To a solution of sodium (1.15 g, 50 mmol) in 200 mL of anhydrous methanol was added the mercaptan 1 (7.2 g, 50 mmol). 2-Bromoethanol (3.9 mL, 6.9 g, 55 mmol) dissolved in 20 mL of anhydrous methanol was added dropwise. After the resulting mixture was allowed to stir overnight, the precipitate was collected and recrystallized from water: yield 6.3 g (67%); mp 231–233 °C (lit.[13] mp 234–235 °C).

5-(Methylthio)uracil (7). To a solution of sodium (0.46 g 20 mmol) in 200 mL of dry methanol was added 2.88 g (20 mmol) of 1. Methyl iodide (3.12 g, 1.37 mL, 20 mmol) was added and the mixture allowed to reflux for 2 h. The resulting precipitate was collected and washed with water and then methanol. Crystallization from water afforded pure material: yield 2.85 g (82%); mp 303–305 °C (lit. 307–308 °C[11] 300 °C dec[12]).

5-(2-Propenylthio)uracil (5). The 5-*S*-allyl derivative 4 (1.0 g, 5.4 mmol) was dissolved in 12.3 mL of Claisen's alkali. The resulting solution was refluxed under nitrogen for 24 h and neutralized with 5 N HCl, and most of the liquid present was removed by evaporation in vacuo. Water (100 mL) was added and the product collected by filtration. Crystallization from ethanol afforded an analytical sample: yield 0.62 g (62%); mp 255–260 °C dec; H^1 NMR (Me_2SO-d_6) δ 7.6 (m, 1 H), 5.8 (m, 2 H), 1.7 (d, J = 5 Hz, 3 H); IR (KBr) 3260 (C=C—H str), 1670 (C=O str) cm^{-1}. Anal. Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.38; N, 15.21. Found: C, 45.60; H, 4.42; N, 15.20.

2*H*,3*H*,6(8)*H*-1,4-Oxathiino[2,3-*d*]pyrimidin-7-one (9). The 5-[(2-hydroxyethyl)thio] derivative 2 (0.94, 5 mmol) was added to 7 mL of concentrated H_2SO_4, and the mixture, protected from moisture, was heated for 1 h on a steam bath. The resulting solution was allowed to cool and poured into ethyl ether. The ether was decanted off and the remaining gummy solid dissolved in 500 mL of H_2O containing 2 g of $NaHCO_3$. The volume of the aqueous solution was reduced to 75 mL in vacuo. The precipitate which formed after the mixture was allowed to stand at 4 °C overnight was collected by filtration and dried at 50 °C in vacuo to afford an analytical sample: yield 0.27 g (32%); mp 198–202 °C; H^1 NMR (Me_2SO) δ 7.8 (s, 1 H, H-6), 4.6 (t, 2 H, J = 5 Hz, OCH_2), 3.1 (t, 2 H, J = 5 Hz, SCH_2); IR (KBr) 1665 cm^{-1} (C=O str). Anal. Calcd for $C_6H_6N_2O_2S$: C, 42.34; H, 6.05; N, 16.46. Found: C, 42.14; H, 6.09; N, 16.20.

1-(2′,3′,5′-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-(allylthio)uracil (11). To 0.92 g (5 mmol) of the *S*-allyl compound 4 in 70 mL of absolute acetonitrile were added 2.52 g (5 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose, 4.06 g (12 mmol) of $C_4F_9SO_3K$, 0.79 mL (3.5 mmol) of hexamethyldisilizane, and then 1.89 mL (15 mmol) of trimethylchlorosilane. The resulting mixture was refluxed for 20 h with careful exclusion of moisture. The mixture was then evaporated to dryness in vacuo, diluted with methylene chloride, and extracted with $NaHCO_3$ and NaCl solutions. Evaporations of the solvent in vacuo gave a tan residue which was recrystallized from ethyl acetate–hexane to give an analytical sample: yield 3.14 g (72%); mp 188–190 °C; H^1 NMR ($CDCl_3$) 8.6 (s, 1 H, H-6), 8.2–7.2 (m, 15 H, COC_6H_5), 6.3 (d, 1 H, J = 6 Hz, H-1′), 6.0–5.3 (m, 3 H, CH_2=CH), 5.2–4.7 (m, 5 H, H-2′, H-3′, H-4′, H-5′), 3.3 (d, 2 H, C=CCH_2); IR (KBr) 1610 (C=C str), 3050 cm^{-1} (=CH_2 str). Anal. Calcd for $C_{33}H_{28}N_2O_9S$: C, 63.05; H, 4.49; N, 4.46. Found: C, 63.18; H, 4.62; N, 4.45.

N^1-(β-D-Ribofuranosyl)-5-(allylthio)uracil (11a). To a suspension of the protected nucleoside 11 (1.0 g, 1.6 mmol) in anhydrous methanol (20 mL) was added a solution of sodium (0.05 g, 2.2 mmol) in methanol (4 mL) under a N_2 atmosphere, and the resulting soltuion was stirred at room temperature for 2 h. Dowex 50W resin (H^+ form, 5 mL, washed with methanol) was added and the mixture stirred for 15 min. The solution was filtered, and a few drops of glacial acetic acid were added. It was then evaporated in vacuo to approximately 4 mL and poured into 40 mL of ether with vigorous stirring. The mixture was allowed to stand overnight at 4 °C and the product collected: 94% yield; mp 152–154 °C; H^1 NMR (D_2O) δ 8.1 (s, 1 H, H-6), 6.0 (d, 1 H^1, J = 5 Hz, 1^1-H), 5.8–4.8 (m, 3 H, CH=CH_2), 4.6–3.2 (m, 5 H, H-2′, H-3′, H-4′, H-5′); IR (KBr) 1605 (C=C str), 3010 cm^{-1} (=CH_2 str). Anal. Calcd for $C_{12}H_{16}N_2O_6S$: C, 45.56; H, 5.10; N, 8.86. Found: C, 45.81; H, 5.19; N, 8.68.

1-(2′,3′,5′-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-(propargylthio)uracil (13). This material was prepared in the same scale and manner as used in the preparation of 11; the propargyl pyrimidine 6 was the starting material. The product formed in 48% yield: mp 200–201 °C; H^1 NMR ($CDCl_3$) 8.0–7.3 (m, 15 H, COC_6H_5), 6.2 (d, 1 H, J = 5 Hz, H-1′), 5.9–4.7 (m, 5 H, H-2′, H-3′, H-4′, H-5′); 3.6 (t, 2 H, J = 2 Hz, CH_2C=C), 3.1 (t, 1 H, J = 2 Hz, C=CH); IR (KBr) 3295 (C=CH); 1705, 1710 cm^{-1} (C=O). Anal. Calcd for $C_{33}H_{26}N_2O_9S$: C, 63.26; H, 4.17; N, 4.47. Found: C, 63.40; H, 4.09; N, 4.25.

N^1-(β-D-Ribofuranosyl)-5-(propargylthio)uracil (13a). Deblocking of 13 to 13a was done in the same manner and scale as in the preparation of 11a from 11. The product formed in 90% yield: mp 123–126 °C; H^1 NMR (D_2O) δ 8.2 (s, 1 H, H-H), 6.1 (d, 1 H, J = 5 Hz, H-1), 3.5 (t, 2 H, J = 3 Hz, CH_2C=C) 3.0 (t, 1 H, J = 3 Hz, C=CH) IR (KBr) 3290 (C=CH); 1700, 1715 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{14}N_2O_6S$: C, 45.88; H, 4.49; N, 8.92. Found: C, 45.52; H, 4.51; N, 9.11.

1-(2′,3′,5′-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-(2-propenylthio)uracil (12). This material was prepared in the same scale and manner as used in the preparation of 11; the propenyl pyrimidine 5 was the starting material. The product formed in 70% yield: mp 143–145 °C; H^1 NMR ($CDCl_3$) δ 8.2–7.2 (m, 15 H, COC_6H_5, H-6), 6.3 (d, 1 H, J = 5 Hz, H-1), 4.8 (s, 2 H, H-5′), 1.8 (d, 3 H, J = 6 Hz, C=CCH_3); IR (KBr) 3170, 1600 (CH=CH), 1710, 1730 cm^{-1} (C=O). Anal. Calcd for $C_{33}H_{26}N_2O_9S$: C, 63.05; H, 4.49; N, 8.86. Found: C, 45.48; H, 4.09; N, 8.82.

N^1-(β-D-Ribofuranosyl)-5-(2-propenylthio)uracil (12a). Deblocking of 12 to 12a was carried out in the same manner and scale as in the preparation of 11a from 11. The product formed in 92% yield: mp 148–151 °C; H^1 NMR (D_2O) 8.3 (s, 1 H, 6-H), 6.1 (d, 1 H, J = 5 Hz), 4.5–4.0 (m, 2 H, CH=CH) 1.9 (d, 3 H, C=CCH_3); IR (KBr) 3050 1600 (CH=CH), 1710, 1660 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{16}N_2O_6S$: C, 45.56; H, 5.10; N, 8.86. Found: C, 45.48; H, 5.10; N, 8.86.

1-(2′,3′,5′-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-(methylthio)uracil (14). This material was prepared in the same scale and manner as those used in the preparation of 11; the *S*-methylpyrimidine 7 was the starting material. The product formed in 48% yield; mp 196–198 °C (lit.[9] mp 202–204 °C).

N^1-(β-D-Ribofuranosyl)-5-(methylthio)uracil (14a). Deblocking of 14 to 14a was done in the same manner and scale as in the preparation of 11a from 11. The product formed in 67% yield; mp 186–187 °C (lit.[9] mp 188–189 °C).

1-(2′,3′,5′-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-(benzylthio)uracil (15). This material was prepared in the same scale and manner as used in the preparation of 11; the *S*-benzylpyrimidine 8 was the starting material. The product formed in

(10) F. J. Dinan and T. J. Bardos, *J. Med. Chem.*, **23**, 569 (1980).
(11) M. P. Kotick, C. Szantay, and T. J. Bardos, *J. Org. Chem.*, **34**, 3806 (1969).
(12) J. M. Carpenter and G. Shaw, J. Chem. Soc., 3987 (1965).
(13) E. K. Ryu, Ph.D. Thesis, Department of Medicinal Chemistry, State University of New York at Buffalo, 1976.

51% yield: mp 159–161 °C; H^1 NMR ($CDCl_3$) 9.3 (s, 1 H, H-6), 8.0–7.0 (m, 20 H, CH_2S) 6.0–5.7 (m, 3 H, H-2′, H-3′, H-4′), 4.6 (s, 2 H, CH_2O), 3.8 (s, 2 H, CH_2S); IR (KBr) Anal. Calcd for $C_{37}H_{30}N_2O_9S$: C, 65.47; H, 4.46; N, 4.13. Found: C, 65.50; H, 4.21; N, 4.21.

N^1-(β-D-Ribofuranosyl)-5-(benzylthio)uracil (15a). Deblocking of **15** to **15a** was done in the same manner and scale as in the preparation of **11a** from **11**. The product formed in 72% yield: mp °C; H^1 NMR (D_2O) δ 7.5 (s, 1 H, H-6), 7.3–7.0 (m, 5 H, C_6H_5), 5.9 (d, 1 H, J = 6 Hz, H-1′), 3.7 (s, 2 H, SCH_2); IR (KBr) Anal. Calcd for $C_{16}H_{18}N_2O_6S$: C, 52.45; H, 4.95; N, 7.65. Found: C, 52.51; H, 4.85; N, 7.69.

1-(2′,3′,5′-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2*H*,3*H*,6(8)*H*-1,4-oxathiino[2,3-*d*]pyrimidin-7-one (16). This material was prepared in the same scale and manner as used in the preparation of **11**; the bicyclic pyrimidine **9** was the starting material. The product formed in 28% yield: mp 214–220 °C dec; ^1H NMR (Me_2SO-d_6) δ 8.8 (s, 1 H, H-6), 8.1–7.2 (m, 15 H, COC_6H_5), 6.1–5.6 (m, 3 H, H-2′, H-3′, H-4′), 4.3 (d, 2 H, J = 5 Hz, CH_2O, 2.9 (d, 2 H, J = 5 Hz, CH_2S); IR (KBr) 2920 (CH_2 str), 1570 cm^{-1} (C=O). Anal. Calcd for $C_{32}H_{26}N_2O_9$: C, 62.54; H, 4.25; N, 4.56. Found: C, 62.40; H, 4.31; N, 4.50.

Acknowledgment. This work was supported by a grant from the Research Corp. (F.J.D.) and PHS Grant No. CA-06695 from the National Cancer Institute (T.J.B.).

Registry No. 1, 14020-53-2; 2, 80822-27-1; 4, 73236-43-8; (*E*)-5, 80822-28-2; (*Z*)-5, 80822-29-3; 6, 73236-44-9; 7, 16350-59-7; 8, 21736-44-7; 9, 80822-30-6; 11, 80822-31-7; 11a, 71106-92-8; (*E*)-12, 80822-32-8; (*Z*)-12, 80822-33-9; (*E*)-12a, 80822-34-0; (*Z*)-12a, 80822-35-1; 13, 80845-38-1; 13a, 80822-36-2; 14, 29979-89-3; 14a, 71106-89-3; 15, 80845-39-2; 15a, 58367-10-5; 16, 80822-37-3; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose, 14215-97-5; 2-bromoethanol, 540-51-2.

Some Addition Reactions of 2-Substituted Quinoxaline 1,4-Dioxides

Makhluf J. Haddadin* and M. Adnan Atfah

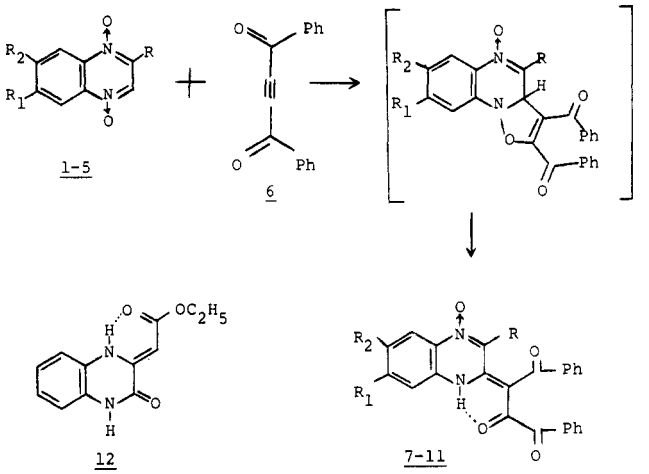
Chemistry Department, American University of Beirut, Beirut, Lebanon

Received September 21, 1981

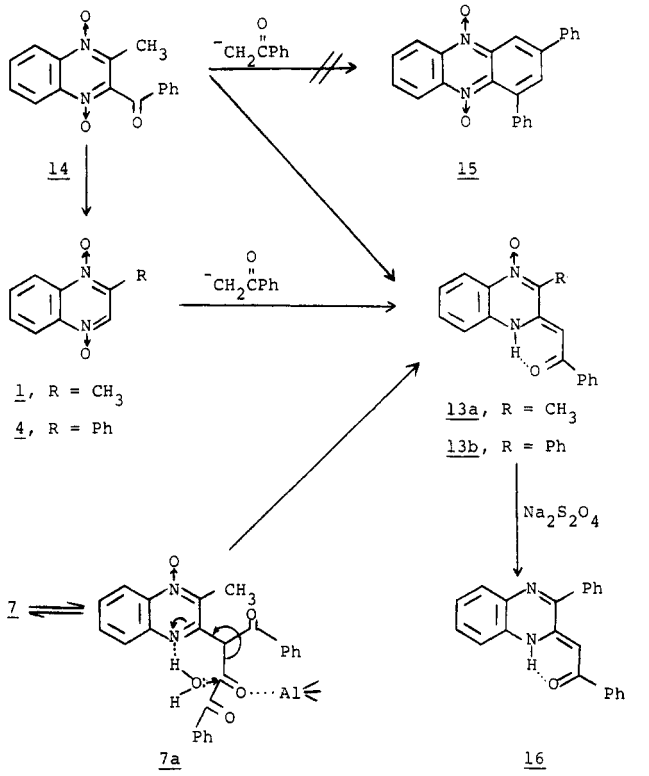
Our interest in the chemistry of quinoxaline 1,4-dioxides and phenazine 5,10-dioxides stems from their properties as antibacterial agents. Indeed, a 2-substituted quinoxaline 1,4-dioxide, methyl 3-[(2-quinoxalinyl)methylene]carbazate 1,4-dioxide, known commercially as Mecadox,[1] has proven to be an effective antibacterial agent. In an earlier paper,[2] we reported the easy conversion of 2,3-dimethylquinoxaline 1,4-dioxides into phenazine 5,10-dioxides. In this work we describe the syntheses of a number of 2,3-disubstituted quinoxaline monoxides from 2-substituted quinoxaline 1,4-dioxides.

Although various cycloaddition reactions of alkynes to heteroaromatic *N*-oxides have been reported,[3] no examples of such reactions that involve quinoxaline 1,4-dioxides are known. We found that treatment of quinoxaline 1,4-dioxides **1–5**, which hold a substituent at position 2 and none at position 3, with dibenzoylacetylene (**6**) in benzene or ethanol at room temperature resulted in the immediate development of a red color and the gradual precipitation of products **7–10** as red solids from the reaction mixture (see Scheme I and Table I). Product **11** was yellow in the crystalline form and red in solution. The progress of the reaction was monitored by TLC, and the reaction was found to be complete in 2–4 days. The yields ranged between 60% and 85% and were improved when the total residue of the reaction mixture was separated by thick-layer chromatography. Comparable yields were obtained when the reactions were carried out in boiling benzene or ethanol.

Scheme I



Scheme II



The infrared spectra of each of products **7–11** showed a broad band at 3300–3100 (hydrogen bonded OH or NH), 1685–1675 (α,β-unsaturated C=O), and 1345–1340 cm^{-1} (N→O). Products **7–11** can exist in tautomeric equilibria; from the intense colors of these adducts, the structure of what is believed to be the predominant tautomer is as shown in Scheme I. Such tautomerism is not without precedent, as quinoxalinones **12** have been reported to possess three tautomeric structures.[4]

Furthermore, in an attempt to purify product **7** by column chromatography on alumina (Merck activity II),

(1) (a) Chas Pfizer and Co U.S. Patent 3 371 090, 1968. Research Corp. U.S. Patent 3 398 141, 1968. (b) Thracher, G. W.; Shively, J. E.; Askelson, C. E.; Babcock, W. E.; Chalquest, R. R. *J. Anim. Sci.* **1970**, *31*, 333.
(2) Issidorides, C. H.; Atfah, M. A.; Sabounji, J. J.; Sidani, A. R.; Haddadin, M. J. *Tetrahedron* **1978**, *34*, 217.
(3) Huisgen, R.; Seidel, H. *Tetrahedron Lett.* **1963**, 2019.
(4) Kurasawa, Y.; Takada, A. *Heterocycles* **1980**, *14*, 281.

0022-3263/82/1947-1772$01.25/0