# Studies on Biologically Active Nucleosides and Nucleotides. 2. A Convenient One-Step Synthesis of 2,2′-Anhydro-1-(3′,5′-di-O-acyl-β-D-arabinofuranosyl)pyrimidines from Pyrimidine Ribonucleosides

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*Received January 25, 1977*

Treatment of cytidine with a number of aliphatic and aromatic carboxylic acid anhydrides in the presence of boron trifluoride etherate in refluxing acetonitrile afforded 3′,5′-diesters (**5a**) of 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine hydrotetrafluoroborate in yields of 42–79%. Carboxylic acid chlorides and carboxylic acids gave similar results when used in place of carboxylic anhydrides. Application of the reaction to uridine was attempted with acetic anhydride to afford 2,2′-anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)uracil in a moderate yield.

The antileukemic,[1] immunosuppressive,[2] and anti-DNA viral activities[3] of 1-(β-D-arabinofuranosyl)cytosine (araC) are well known. In attempts to find derivatives of greater activity and selectivity various modifications of the cytosine ring and the sugar moiety have been made. Among compounds recently investigated 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine (anhydro-ara-C)[4] and its 3′,5′-di-O-acyl derivatives[5] are particularly interesting because of their high antitumor potency and resistance to cytidine deaminase.

In a previous report[6] from this laboratory, the reaction of tetraacetoxysilane with pyrimidine ribonucleosides in the presence of acid catalyst was shown to yield 2,2′-anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)pyrimidine nucleosides. The reaction mechanism was interpreted to involve monoacetylation of one of the vicinal hydroxyls as a result of participation by the silyl group, followed by the formation of a 2′,3′-acetoxonium ion. The 2′,3′-acetoxonium ion then reacts intramolecularly with the $C_2$-carbonyl oxygen to afford the 2,2′-anhydronucleoside.

From these mechanistic considerations it was envisaged that it might be possible to accelerate acetoxonium ion formation at the expense of acetylation of the remaining hydroxyl, provided a suitable catalyst was employed. If this were possible even unselective acylating reagents might be used successfully. Accordingly, we attempted the reaction of a pyrimidine ribonucleoside with various acylating reagents in the presence of a Lewis acid catalyst with the hope of developing a convenient method for the preparation of 2,2′-anhydro-1-(3′,5′-di-O-acyl-β-D-arabinofuranosyl)pyrimidine nucleoside.

**Reactions with Carboxylic Acid Anhydrides.** A preliminary reaction was run by mixing cytidine (1) with acetic anhydride (3 molar equiv) and boron trifluoride etherate (3 molar equiv) as a catalyst in acetonitrile, and then heating the resulting solution gradually to reflux. The reaction could be conveniently monitored by ultraviolet (UV) spectroscopy in acidic media. As it proceeds the UV maximum of 1 at 280 nm should be changed to double maxima at approximately 231 and 263 nm, the characteristic maxima of the anhydro-ara-C chromophore.[7] The UV spectrum of the reaction mixture after 15 min heating showed a maximum at 275 nm. Examination of the crude product by NMR indicated it to be roughly a 2:1 mixture of 2′,3′,5′-tri-O-acetylcytidine[8] (**6**, R = $CH_3$) and 2,2′-anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)-cytosine hydrotetrafluoroborate (**5a**, R = $CH_3$). It seemed likely that the competing peracetylation predominated at the expense of 2′,3′-acetoxonium ion formation under these reaction conditions. This result reminded us of our previous observation[6] where formation of 3′,5′-di-O-acetyl anhydro-ara-C from cytidine and tetraacetoxysilane in the presence of boron trifluoride etherate was found to be very slow below 50 °C. Therefore, it was presumed that the rate of 2′,3′-acetoxonium ion formation could surpass the rate of peracetylation, if the reaction was kept at reflux throughout. Thus, the reaction was conducted by adding acetic anhydride to a boiling solution of cytidine and boron trifluoride etherate in acetonitrile. Within 5 min the reaction was essentially complete. The UV spectrum exhibited double maxima at 232 and 265 nm, indicating predominant formation of **5a** (R = $CH_3$). The presence of a negligible amount of 2′,3′,5′-tri-O-acetylcytidine was observed on TLC. Evaporation of the solvent followed by crystallization by trituration with ether gave crude product, which upon recrystallization from ethanol afforded pure **5a** (R = $CH_3$) in 67% yield. Other Lewis acids such as ferric chloride and antimony pentachloride could also be used as catalyst but were not as effective as boron trifluoride etherate. The fairly good yield and simplicity of the isolation method prompted us to extend this reaction to the preparation of homologous 3′,5′-di-O-acyl anhydro-ara-C derivatives. The reactions were performed under the same conditions, and isolation of the crude product was readily achieved by concentrating the reaction mixture, followed by crystallization of the residue from an appropriate solvent. Recrystallization of the crude product from an appropriate solvent gave **5a** in yields of 42–79%. In general the lower acyl derivatives could be readily isolated in pure form in higher yields than the longer acyl derivatives. The rather low yields of the long chain esters were mainly due to the difficulty in the separation of the esters from the liberated carboxylic acids. The structures of the representative compounds listed in Table I were confirmed by their elemental analyses and by NMR spectra. In addition, all of the diesters other than those containing a conjugated double bond system in the acyl moiety gave UV spectra characteristic of anhydro-ara-C. The spectral features of 3′,5′-di-O-acyl anhydro-ara-C and related compounds prepared by the acylation of anhydro-ara-C in dimethylacetamide have recently been described by Moffatt et al.[5] The 3′,5′-di-O-acyl anhydro-ara-C hydrotetrafluoroborate salt could be converted to the hydrochlorides (**5b**) by passing them (in aqueous methanol or aqueous tetrahydrofuran) through a column of anion-exchange resin ($Cl^-$ form). A distinct spectral difference between **5a** and **5b** was observed with regard to the NH stretching vibration band in the infrared (IR) spectrum. Thus, the IR spectrum of **5a** shows sharp bands (generally three peaks) between 3200 and 3440 $cm^{-1}$, while **5b** shows a broad unsolved band which overlaps the CH stretching band of Nujol in the region of 3050–3280 $cm^{-1}$.

The mechanism of the conversion of cytidine to 3′,5′-di-

**Table I. 3′,5′-Diacyl Derivatives of 2,2′-Anhydro-1-(β-D-arabinofuranosyl)cytosine Hydrotetrafluoroborate (5a)**

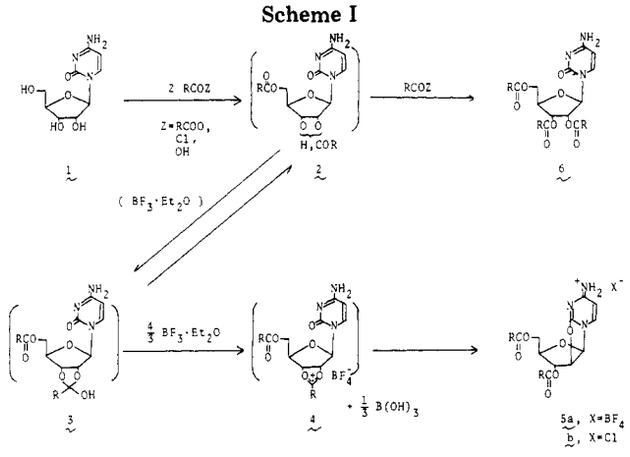
| Registry no. | Acyl group | Composition[a] | Mp, °C | Method[b] | Yield,[c] % | Recrystn solvent | UV (MeOH), $\lambda_{max}$ (ε) |
|---|---|---|---|---|---|---|---|
| 62840-04-4 | Acetyl | $C_{13}H_{16}N_3O_6BF_4 \cdot H_2O$ | 150–151 | A | 67 | EtOH | 235 (10 400) |
| | | | | B | 61 | | 264 (11 800) |
| 62757-81-7 | *n*-Valeryl | $C_{19}H_{28}N_3O_6BF_4 \cdot 0.5H_2O$ | 171–173 | A | 71 | EtOH | 236 (10 000) |
| | | | | | | | 264 (11 600) |
| 62757-83-9 | Isovaleryl | $C_{19}H_{28}N_3O_6BF_4 \cdot H_2O$ | 210–212 | A | 55 | EtOH | 235 (10 500) |
| | | | | | | | 264 (12 000) |
| 62757-85-1 | *sec*-Valeryl | $C_{19}H_{28}N_3O_6BF_4 \cdot 0.5H_2O$ | 183–185 | B | 63 | EtOH | 236 (10 800) |
| | | | | | | | 264 (12 700) |
| 62757-87-3 | Pivaloyl | $C_{19}H_{28}N_3O_6BF_4$ | 243–244 | A | 79 | $H_2O$ | 237 (10 300)[d] |
| | | | | B | 56 | | 264 (12 200) |
| | | | | C | 52 | | |
| 62840-06-6 | Decanoyl | $C_{29}H_{48}N_3O_6BF_4 \cdot 0.5H_2O$ | 75–92 | B | 64 | MeOH | 235 (10 200)[d] |
| | | | | | | | 264 (11 400) |
| 62757-89-5 | Margaroyl | $C_{43}H_{76}N_3O_6BF_4 \cdot 0.5H_2O$ | 137–138 | B | 78 | EtOH | 235 (10 000) |
| | | | | C | 64 | | 264 (11 600) |
| 62757-91-9 | Lignoceroyl | $C_{57}H_{104}N_3O_6BF_4$ | 204 | B | 61 | THF | 235 (10 000) |
| | | | | | | | 264 (11 500) |
| 62757-93-1 | Cyclopropane-carbonyl | $C_{17}H_{20}N_3O_6BF_4 \cdot H_2O$ | 221–223 | A | 42 | EtOH | 235 (10 200) |
| | | | | | | | 264 (11 600) |
| 62757-95-3 | 1-Adamantoyl | $C_{31}H_{40}N_3O_6BF_4$ | 285–286 | A | 64 | MeOH | 236 (11 500) |
| | | | | B | 76 | | 264 (13 400) |
| 62757-97-5 | Crotonoyl | $C_{17}H_{20}N_3O_6BF_4$ | 189–191 | A | 43 | *i*-PrOH | 264 (11 000) |
| 62840-07-7 | Benzoyl | $C_{23}H_{20}N_3O_6BF_4 \cdot 0.5H_2O$ | 280–283 | A | 63 | MeOH | 233 (35 700) |
| | | | | B | 57 | | 265 (13 200) |
| | | | | C | 60 | | |
| 62757-99-7 | γ-Phenyl-butyryl | $C_{29}H_{32}N_3O_6BF_4$ | 103–105 | A | 42 | *i*-PrOH | 237 (9300)[d] |
| | | | | | | | 264 (10 700) |
| 62758-01-4 | Cinnamoyl | $C_{27}H_{24}N_3O_6BF_4$ | 255 | A | 46 | MeOH | 217 (37 500) |
| | | | | | | | 223 (30 800) |
| | | | | | | | 278 (49 600) |

[a] All compounds analyzed correctly for C, H, and N. In the case of the diacetyl ester, F was also analyzed: calcd, 18.31; found, 18.22. [b] A, acid anhydride; B, acid chloride; C, carboxylic acid. [c] The yields are all calculated on the isolated pure product. [d] Measured in EtOH.

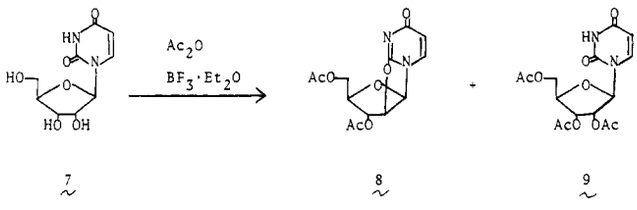
*O*-acyl anhydro-ara-C most likely involves formation of 2′,3′-acyloxonium ion **4** as an intermediate. Subsequent intramolecular attack at C-2′ by the C-2 carbonyl oxygen would then give 3′,5′-di-*O*-acyl anhydro-ara-C. The 2′,3′-acyloxonium ion **4** can be envisaged to have formed via ring closure of the 2′(3′),5′-di-*O*-acylated nucleoside. Attack of the 2′(3′)-hydroxyl on the adjacent acyl group could be facilitated through coordination to boron trifluoride.[9] The reaction should proceed competitively in two directions: one to the 2′,3′-acyloxonium ion and another to 2′,3′,5′-tri-*O*-acylcytidine (**6**). However, the result of the experiment indicated that the 2′,3′-acyloxonium ion formation proceeded much faster than the peracylation at a temperature around 80 °C, whereas at low temperature peracylation predominated. In addition to its role as a catalyst for formation of intermediate **3**, boron trifluoride etherate could function as a dehydroxylating agent in the conversion of **3** to **4**. In this respect the equilibrium between diacylated intermediate **2** and ortho ester **3** would be shifted to the right by removal of hydroxyl (Scheme I). The formation of acyloxonium ion from ortho esters using boron trifluoride[10a] or its ether complex[10b] has been demonstrated.

A similar result was obtained when the reaction was applied to uridine (**7**). Treatment of **7** with acetic anhydride in the presence of boron trifluoride etherate in refluxing acetonitrile gave 2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)uracil[6] (**8**) and 2′,3′,5′-tri-*O*-acetyluridine[6] (**9**) in 65 and 4% yield, respectively (Scheme II). It may be noted that the cleavage of the anhydro bond has been reported by Holý[11] via treatment of 2,2′-anhydro-3′,5′-di-*O*-acyluridine with boron trifluoride etherate in refluxing methanol. We have observed the same phenomenon[6] in the treatment of **8** with zinc chloride in acetic acid. However, cleavage of the anhydro bond would not occur in acetonitrile because of the low nucleophilicity of acetonitrile, and reaction with the liberated carboxylic acid would be minimized because of its low concentration in the aprotic reaction solvent.

**Scheme I**



**Scheme II**



**Reactions with Carboxylic Acid Chlorides.** The facile preparation of 3′,5′-di-*O*-acyl anhydro-ara-C's by the anhy-

dride method described above prompted us to examine this reaction with the corresponding carboxylic acid chlorides. It may be noted that the preparation of 2,2′-anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)cytosine hydrobromide via reaction of cytidine with acetyl bromide in refluxing acetonitrile (40% yield) has recently been described by Marumoto and Honjo.[12] However, it seems difficult to extend their method to higher homologues of 3′,5′-di-O-acetyl anhydro-ara-C.[5]

As expected treatment of cytidine with different carboxylic acid chlorides (3 molar equiv) in the presence of boron trifluoride etherate (3 molar equiv) in refluxing acetonitrile resulted in the formation of **5a** in yields of 56–78% (see Table I). Once again the reactions took place quite rapidly and the products were isolated by the simple workup as described in the anhydride method. Somewhat lower yields were obtained in the case of short-chain esters compared to the anhydride method. However, relatively better yields were obtained in a series of longer chain esters, since the difficulty in separating the product from the carboxylic acid liberated was eliminated in this case. In the case of benzoyl chloride, a small amount of a by-product which corresponds to a faster moving spot on TLC (silica gel) was isolated in crystalline form by chromatographic separation on silica gel. This compound was identified as 2′,3′,5′-tri-O-benzoylcytidine (**6**, R = $C_6H_5$) by its NMR spectrum.

**Reactions with Carboxylic Acids.** It is well known that boron trifluoride etherate functions as an effective reagent in a direct esterification of carboxylic acids.[13] In view of the mechanim of the present reaction, it was quite natural to consider that the reaction of cytidine with carboxylic acid in the presence of boron trifluoride etherate should also afford **5a** following subsequent steps. After some experimentation it was found that the reactions with carboxylic acids were slow, and required longer refluxing time (1–3 h) and larger excess amount of the reagents (3–9 molar equiv, depending on the nature of the carboxylic acid used). As shown in Table I, the 3′,5′-diesters of anhydro-ara-C were prepared in moderate yields by this method.

The work presented in this paper provides a convenient method for the synthesis of a wide range of 3′,5′-di-O-acyl anhydro-ara-C's by a single-step reaction from cytidine.

## Experimental Section

Infrared spectra were obtained on a Shimadzu IR-27G spectrophotometer. $^1H$ NMR spectra were obtained with a Hitachi Perkin-Elmer R-20A spectrometer; chemical shifts are reported in δ units using tetramethylsilane as an internal reference. UV spectra were measured on a Hitachi EPS-3T spectrometer. Column chromatography was done using Merck silica gel (0.05–0.20 mm particle size).

**Materials.** Boron trifluoride etherate was purified by distillation according to the method of Zweifel and Brown.[14] Acetonitrile was dried over magnesium sulfate and distilled after being refluxed with phosphorus pentoxide.

**General Procedure for the Preparation of 2,2′-Anhydro-1-(3′,5′-di-O-acyl-β-D-arabinofuranosyl)cytosine Hydrotetrafluoroborate (5a). 2,2′-Anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)cytosine Hydrotetrafluoroborate (5a, R = $CH_3$). By Anhydride Method (Method A).** A solution of acetic anhydride (6.3 g, 61.8 mmol) in acetonitrile (50 mL) was added dropwise to a stirred refluxing solution of cytidine (5.0 g, 20.6 mmol) and boron trifluoride etherate (7.8 mL, 61.8 mmol) in acetonitrile (150 mL) at such a rate (ca. 10 min) as to maintain refluxing. After the addition was completed, the reaction mixture was maintained at the reflux temperature for 5 min and then cooled immediately. The mixture was concentrated to dryness in vacuo below 40 °C. The residue was triturated with ether (200 mL) and then with 2-propanol (20 mL). 2-Propanol (20 mL) was added to the triturated residue, and the mixture was allowed to stand overnight in a refrigerator. The resulting crystals were recrystallized from EtOH to give 5.7 g (67%) of **5a** (R = $CH_3$) with mp 148–150 °C. An analytical sample had mp 150–151 °C: NMR ($Me_2SO$-$d_6$) δ 1.90 (s, 3, OAc), 2.14 (s, 3, OAc), 3.9–4.5 (m, 2, $C_{5'}$ $H_2$), 4.6–4.9 (m, 1, $C_{4'}$ H), 5.3–5.6 (m, 1, $C_{3'}$ H), 5.77 (d, 1, $J$ = 6 Hz, $C_{2'}$ H), 6.58 (d, 1, $J$ = 7.5 Hz, $C_5$ H), 6.64 (d, 1, $J$ = 6 Hz, $C_{1'}$ H), 8.36 (d, 1, $J$ = 7.5 Hz, $C_6$ H), 9.2–9.6 (br s, 2, $NH_2$); IR $\nu_{max}$ (Nujol) 3280–3440, 1756, 1748, 1668 $cm^{-1}$. The UV spectrum is described in Table I. Anal. Calcd for $C_{13}H_{16}N_3O_6BF_4 \cdot H_2O$ (415.13): C, 37.61; H, 4.36; N, 10.12; F, 18.31. Found: C, 37.27; H, 4.22; N, 10.11; F, 18.22.

**2,2′-Anhydro-1-(3′,5′-di-O-benzoyl-β-D-arabinofuranosyl)-cytosine Hydrotetrafluoroborate (5a, R = $C_6H_5$). A. By Method B.** A solution of benzoyl chloride (7 g, 49.6 mmol) in acetonitrile (40 mL) was added dropwise to a stirred refluxing solution of cytidine (4.0 g, 16.5 mmol) and boron trifluoride etherate (6.2 mL, 49.6 mmol) in acetonitrile (120 mL) over a period of 10 min. After the addition was completed, the mixture was kept at the reflux temperature for 5 min and then concentrated to dryness in vacuo. The residue was triturated with ether (70 mL) and the resulting crystals were collected by filtration. The crystals were washed with EtOH (50 mL) and recrystallized from MeOH to give 5.0 g (57%) of **5a** (R = $C_6H_5$) with mp 280–283 °C dec: NMR ($Me_2SO$-$d_6$) δ 4.4–4.7 (m, 2, $C_{5'}$ $H_2$), 4.8–5.2 (m, 1, $C_{4'}$ H), 5.7–5.9 (m, 1, $C_{3'}$ H), 6.04 (d, 1, $J$ = 6 Hz, $C_{2'}$ H), 6.53 (d, 1, $J$ = 7.5 Hz, $C_5$ H), 6.69 (d, 1, $J$ = 6 Hz, $C_{1'}$ H), 7.3–8.2 (m, 10, 2 Ar), 8.37 (d, 1, $J$ = 7.5 Hz, $C_6$ H), 9.1–9.5 (br s, 2, $NH_2$). Anal. Calcd for $C_{23}H_{20}N_3O_6BF_4 \cdot 0.5H_2O$ (530.26): C, 52.10; H, 3.99; N, 7.92. Found: C, 51.73; H, 4.02; N, 7.84.

A portion (¼) of the EtOH washings was concentrated to dryness, and the residue (0.7 g) was chromatographed on a column of silicic acid using $CHCl_3$–MeOH (95:5). Evaporation of the fractions which contained less polar substance (monitored by TLC) followed by crystallization of the residue from 2-propanol gave 0.15 g of 2′,3′,5′-tri-O-benzoylcytidine with mp 186–187 °C: NMR ($CDCl_3$) δ 4.6–4.9 (m, 3, $C_{5'}$ $H_2$, $C_{4'}$ H), 5.8–6.3 (m, 4, $C_{3'}$ H, $C_{2'}$ H, $C_{1'}$ H, $C_5$ H), 7.2–8.3 (m, 18, 3 Ar, $NH_2$, $C_6$H); UV $\lambda_{max}$ (MeOH) 232 nm (ε 43 600), 272 (10 600). Anal. Calcd for $C_{30}H_{25}N_3O_8 \cdot 0.5H_2O$ (564.56): C, 63.82; H, 4.64; N, 7.44. Found: C, 64.29; H, 4.71; N, 7.46.

**B. By Carboxylic Acid Method (Method C).** Benzoic acid (6.0 g, 49.2 mmol) was added portionwise to a stirred refluxing solution of cytidine (2.0 g, 8.2 mmol) and boron trifluoride etherate (9.4 mL, 74.5 mmol) in acetonitrile (60 mL) over a period of 5 min. The mixture was kept at the reflux temperature for 3 h and then concentrated to dryness in vacuo. The residue was triturated with ether (150 mL), and the resulting crystals were collected by filtration. The crystals were washed with EtOH (20 mL) and recrystallized from MeOH, giving 2.6 g (60%) of **5a** (R = $C_6H_5$) with mp 279–280 °C dec. The compound was identified with the sample prepared by method B.

**Preparation of 2,2′-Anhydro-1-(3′,5′-di-O-acyl-β-D-arabinofuranosyl)cytosine Hydrochloride (5b) from 5a. A Typical Example.** A solution of **5a** (R = $CH_3$) (2 g, 4.8 mmol) in $H_2O$ (10 mL) was passed through a column of Diaion SA-11B ($Cl^-$, 50 mL), and the column was washed with $H_2O$ (100 mL). The combined eluate and washings were concentrated to dryness in vacuo, giving 1.6 g (92%) of **5b** (R = $CH_3$) with mp 218–219 °C dec: IR $\nu_{max}$ (Nujol) 3120–3280, 1765, 1743, 1678, 1649 $cm^{-1}$. This was identical with an authentic sample[6] by the criteria of IR and NMR spectra.

In the cases of hydrotetrafluoroborate salts with poor solubility in $H_2O$, the salts were dissolved in aqueous organic solvents (50–70% MeOH or 50–60% tetrahydrofuran), and passed through a column of Diaion SA-11B ($Cl^-$).

**Reaction of Uridine with Acetic Anhydride in the Presence of Boron Trifluoride Etherate.** A solution of acetic anhydride (6.3 g, 61.8 mmol) in acetontrile (50 mL) was added dorpwise to a stirred refluxing solution of uridine (5 g, 20.5 mmol) and boron trifluoride etherate (8 mL, 63.4 mmol) in acetontrile (100 mL) at such a rate (5 min) as to maintain refluxing. After the addition was completed, the mixture was cooled and concentrated to dryness in vacuo. The residue was poured into saturated aqueous sodium bicarbonate (150 mL), and the solution was applied to a column of activated charcoal (50 g). The column was washed with $H_2O$ (500 mL) and eluted with EtOH–pyridine (4:1). The eluate (800 mL) was concentrated to dryness in vacuo, and the residue was crystallized from EtOH, giving 4.1 g (65%) of 2,2′-anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)uracil (**8**) with mp 184–186 °C. Identity was established by comparison of the IR and UV spectra with those obtained from an authentic sample,[6] mp 185–186 °C. Storage of the mother liquor from the recrystallization in a refrigerator gave 0.3 g (4%) of 2′,3′,5′-tri-O-acetyluridine (**9**) with mp 129–130 °C which was identical with an authentic sample.[6]

**Acknowledgment.** The authors wish to express their thanks to Drs. Ichiro Chibata and Muneji Miyoshi for their encouragement in this study. They are also indebted to Professor D. E. Bergstrom (University of California, Davis, Calif.) for his helpful suggestions in preparing the manuscript.

**Registry No.**—**5b** (R = Me), 50896-84-9; **8**, 28309-53-7; **9**, 4105-38-8; acetyl chloride, 75-36-5; valeric anhydride, 2082-59-9; isovaleric anhydride, 1468-39-9; *sec*-valeryl chloride, 5856-79-1; pivaloyl chloride, 3282-30-2; pivalic anhydride, 1538-75-6; pivalic acid, 75-98-9; decanoyl chloride, 112-13-0; margaroyl chloride, 40480-10-2; margaric acid, 506-12-7; lignoceroyl chloride, 58576-73-1; cyclopropanecarboxylic anhydride, 33993-24-7; 1-adamantanecarboxylic anhydride, 42601-02-5; 1-adamantoyl chloride, 2094-72-6; crotonic anhydride, 623-68-7; benzoic anhydride, 93-97-0; γ-phenylbutyric anhydride, 1940-02-9; cinnamic anhydride, 538-56-7; acetic anhydride, 108-24-7; cytidine, 65-46-3; boron trifluoride, 7637-07-2; benzoyl chloride, 98-88-4; 2′,3′,5′-tri-*O*-benzoylcytidine, 31652-74-1; benzoic acid, 65-85-0; uridine, 58-96-8.

## References and Notes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# Acyclic Polyhalogenated Monoterpenes from the Red Alga *Plocamium violaceum*


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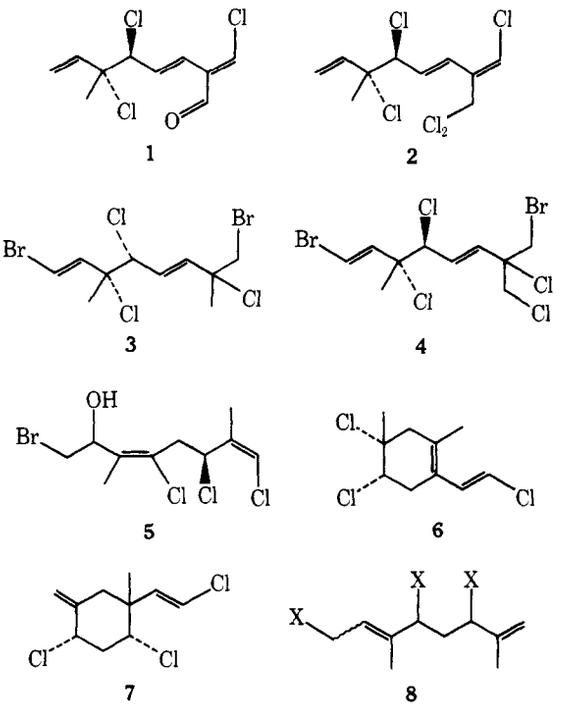
*Received January 24, 1977*


Several new acyclic 1,4,6-trichloro-3,7-dimethyl-2,7-octadiene monoterpenes are reported from the red marine alga *Plocamium violaceum* (Dixon) collected along a narrow coastal region of Monterey County, Calif. Both the gross structures and all of the stereochemical features of these halocarbons were established by extensive analysis of their $^1H$ and $^{13}C$ NMR data in comparison to data from numerous model compounds.


Our recent study of the natural products from the marine algae of the Plocamiaceae has revealed a fascinating array of halogenated monoterpenes. Without exception, every Plocamiaceae species that we have examined has been rich in one or more of these natural products.[1] For example, *Plocamium cartilagineum* (Dixon) contains several 2,7-dimethyl-1,5,7-octatrienes such as cartilagineal **1**[2] or **2**.[3] Other unusual acyclic monoterpenes including **3** and **4** can be isolated from *Plocamium oregonum* (Doty),[4] and costatol (**5**) is found in *Plocamium costatum* (C. Ag.).[5] By contrast, *Plocamium violaceum* (Farlow) has been a source for a number of alicyclic monoterpenes[6,7] such as plocamene B (**6**) and plocamene D (**7**).

Our past work upon the monocyclic constituents from *P. violaceum* has involved specimens toxic to both fish and insects which are collected from a broad area north of Santa Cruz, Calif. (Santa Cruz and San Mateo Counties). Concurrent work by others has shown that *P. violaceum* from San Diego County, Calif., contains additional examples of cyclic monoterpenes.[8] Not long ago we had occasion to collect samples of *P. violaceum* from a narrow coastal region of Monterey County just south of Santa Cruz, Calif. These seaweeds displayed no alicyclic monoterpenes and instead yielded several new acyclic monoterpenes. Reported below are the structures of these interesting new compounds.

Collections of *P. violaceum* from Pescadero Point, Point Joe, and Asilomar Beach (all in Monterey County, Calif.) gave crude oils, from $CHCl_3$ extraction of fresh plants, having fairly




a, X = $ClBr_2$

b, c, X = $Cl_3$