versity of California at Santa Cruz, are gratefully acknowledged by A.C.W.

Registry No.—**3a,** 30859-86-0; **3b,** 14674-46-5; **3c,** 53153-56-3; **3d,** 33721-50-5; **3e,** 1226-43-3; **3f,** 15857-21-3; **3g,** 53153-57-4; **3h,** 35787-02-1; **10a,** 970-31-0; **10b,** 6233-05-2; **10c,** 53153-58-5; **16,** 53153-59-6; **17,** 921-14-2; benzoyl chloride, 98-88-4.

References and Notes

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Synthesis and Properties of *N*-(2,3,5-Tri-*O*-acetyl-D-ribofuranosyl)maleimide

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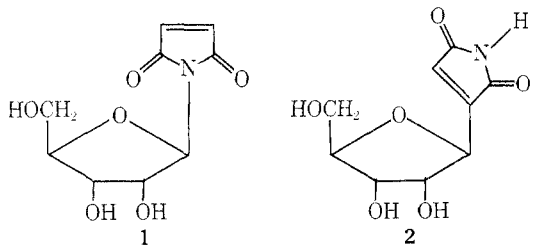
Reaction of silver maleimide with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride afforded *N*-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)maleimide (**5**). The removal of the blocking acetyl groups to obtain the N-substituted analog of showdomycin was not possible owing to its instability. In water, **5** hydrolyzed to maleimide and 2,3,5-tri-*O*-acetyl-D-ribofuranose. In contrast, dissolution in methanol caused the maleimide ring to open, yielding the methyl ester of *N*-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)maleamic acid (**6**). Compound **5** was found to be a good storage form of a reactive ribofuranose derivative. It underwent transglycosylation reactions readily in boiling nitromethane. In this manner, adenosine and cytidine were prepared using N^6-benzoyladenine and N^4-acetylcytosine, respectively. *N*-(2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl)maleimide was also prepared; only in this case mercuric maleimide was the reactant of choice. In addition, the preparation of *N*-trimethylsilylmaleimide and N^4-adamantoylcytosine are described.

The preparation of *N*-β-D-ribofuranosylmaleimide (**1**) was undertaken because such a compound would be an N-substituted analog of the naturally occurring antibiotic, showdomycin (**2**, 2-β-D-ribofuranosylmaleimide, Chart I).[2] Since there is a structural similarity between **1** and **2**, it was thought that the N-substituted analog would be a biologically active substance, perhaps more so than showdomycin, but still maintain some of the biological selectivity of the latter. Recognizing that compound **1** could be a more powerful sulfhydryl reagent than **2**,[3] it was of interest to determine if the ribofuranose ring would confer specificity of binding to enzymes of nucleic acid metabolism and allow the compound to act, in part, as an N-substituted maleimide. Such compounds would have a potential use as antitumor and antimicrobial agents[4] and could conceivably function as "active-site-directed irreversible inhibitors."[5]

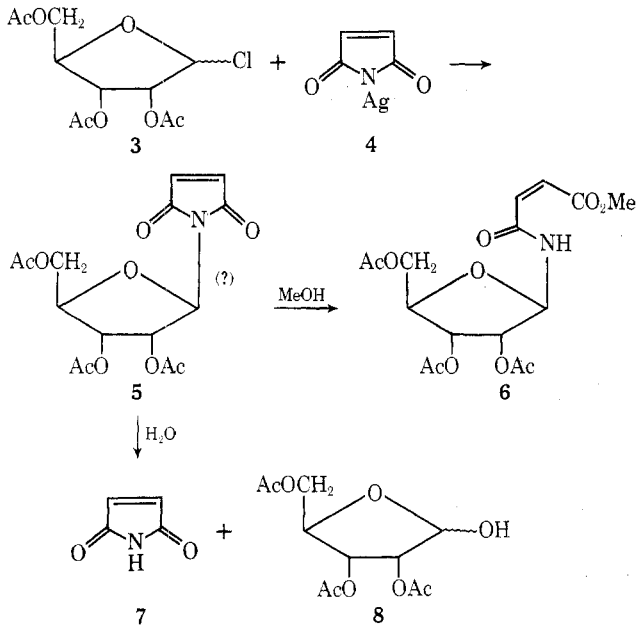
Chart I



1 2

The preparation of silver maleimide and its use in the formation of N-substituted aralkylmaleimides was recently reported.[6] Reaction of silver maleimide (**4**) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride (**3**) in hot benzene gave the blocked product, *N*-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)maleimide (**5**, Scheme I). Unless great care is utilized in the preparation of the chloride **3**, and yields are maximized, the product **5** will be contaminated with unreacted tetra-*O*-acetyl-D-ribofuranose, an undesirable situation since purification by many of the standard procedures, as discussed below, is virtually impossible without degradation of

Scheme I

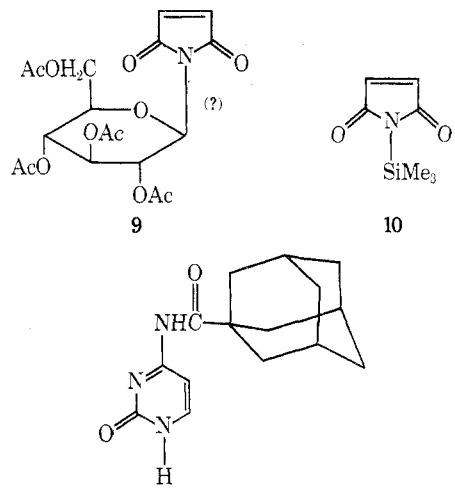


the product. For this reason, a modification of the procedure of Piskala and Šorm[7] was used in the preparation of **3**, which gave superior results over other preparations involving reaction of tetra-*O*-acetyl-D-ribofuranose with hydrogen chloride. Although **5** was not obtained in crystalline form, proof of its structure was confirmed by elemental analysis, uv, ir, and nmr spectra, and homogeneity was further demonstrated by tlc. The ir spectrum of **5** had peaks typical for an N-substituted maleimide at 5.81, 12.04, and 14.45 μ.[6] In contrast, the peaks typical of free maleimide at 3.03 and 14.75 μ were not observed and are a further indication of the purity of the product.[6] The nmr spectrum showed a clean doublet at δ 6.07 which was a good indication that only one anomer was present. Unfortunately, we have not been able to elucidate the anomeric configuration of **5**. The well-known and often quoted trans rule[8] would predict that the product was β; however, the optical rotation (+121°) indicated that the opposite was true and that the configuration was α. The latter would only be the case if Hudson's Isorotation rules were followed, but such an assumption is no longer valid with nucleoside-like compounds.[9] The anomeric coupling constant (J = 4 Hz) does not shed any additional light on this problem since a β-D configuration can only be implied by coupling constants below 3.5 Hz, but can only be unequivocally established at values less than 1.0 Hz.[10]

The problem of removing the blocking acetyl groups was recognized early in the synthetic design. The maleimide moiety should be unstable in a basic medium and there was a good probability that the *N*-glycosyl bond would be unstable in acid. Quite unexpectedly, **5** was found to be susceptible to hydrolysis simply by shaking in water. Although **5** was rather insoluble in water, the products of hydrolysis were soluble and the aqueous solution could be assayed for the appearance of maleimide either by gas chromatography or by uv. The half-life was estimated to be about 1 hr and the products of the hydrolysis, maleimide (**7**) and 2,3,5-tri-*O*-acetyl-D-ribofuranose (**8**), were isolated and identified. In contrast to this behavior in water, a solution of **5** in benzene or chloroform could be washed many times with water without noticeable degradation. Partial degradation was noticed on preparative tlc plates, but not on the analytical tlc plates used in this study. Vacuum distillation of **5** caused extensive decomposition. Maleimide crystals (mp 93–95°) sublimed and then a liquid substance distilled over, whose identity has not been established, but which is probably the elimination product.

Simultaneously with the preparation of **5**, the preparation of *N*-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)-maleimide (**9**, Chart II) was undertaken. When 2,3,4,6-

Chart II



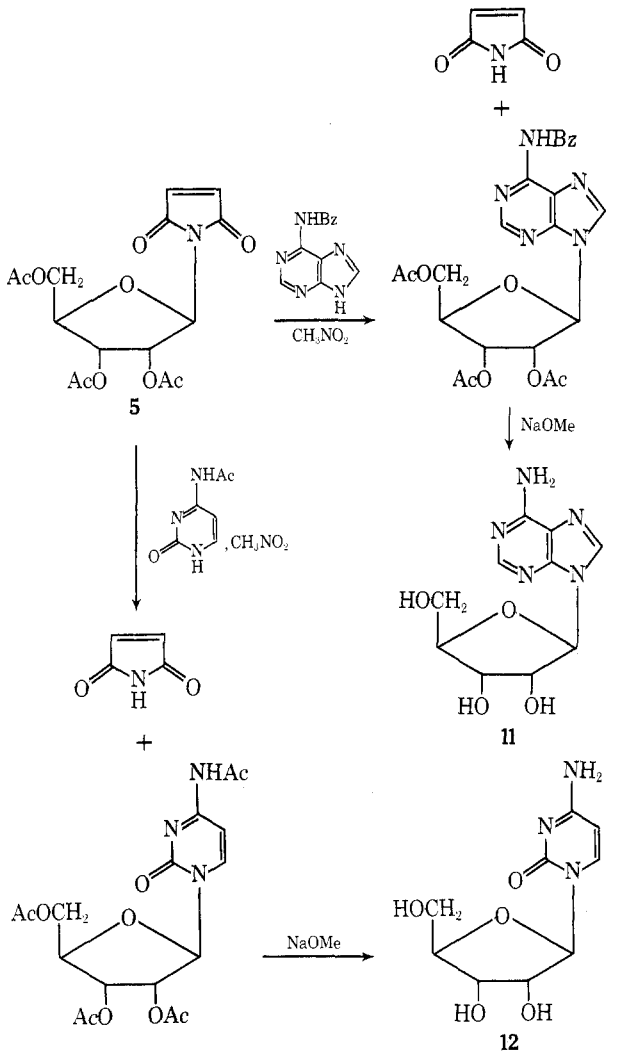
tetra-*O*-acetyl-α-D-glucopyranosyl bromide was reacted with silver maleimide in hot benzene, extensive decomposition occurred. At room temperature, no N substitution took place although a product was formed which may have been the O isomer.[6] However, it was not isolated or identified. Successful coupling was achieved by using mercuric maleimide[6] instead of silver maleimide, and a 36% yield of **9** was obtained following its purification by preparative tlc. Proof of structure was similar to that of **5**. In contrast to the ribosyl derivative **5**, the nmr spectrum of **9** appears to present a good argument concerning the anomeric configuration. A distinct doublet at δ 5.85 indicated that only one anomer was present and the low coupling constant (J = 4 Hz) is suggestive of an α configuration.[10-12] Compound **9** exhibited many of the properties of **5**, being slowly hydrolyzed in water to maleimide and 2,3,4,6-tetra-*O*-acetyl-D-glucose, which were isolated and identified by ir and nmr data. Compound **9** was very unstable on silicic acid columns and only the hydrolytic products were eluted.

Prior to the successful synthesis of either **5** or **9**, a number of coupling procedures were attempted based upon literature methods, which were recently reviewed by Zorbach.[13] The methods employed included the fusion of maleimide with the peracetylated sugar under acid catalysis, coupling of the gylcosyl halide with maleimide utilizing mercuric cyanide as the acid acceptor and nitromethane as the solvent, and the reaction of *N*-trimethylsilylmaleimide (**10**) with the glycosyl halides under various conditions. None of these reactions were successful, although in a few cases, traces of products could be detected on tlc plates.

As yet no method has been devised for the removal of the acetyl groups and another approach will probably have to be used for the synthesis of **1**. It may be advantageous not to have a 2′-acyloxy group because this group could be aiding the ionization of **5** in water by forming a 1,2-orthoacetate ion. A nonparticipating group may, therefore, help stabilize the *N*-glycosylic bond. Experiments along these lines are in progress.

Due to the interesting property of hydrolysis exhibited by **5**, it seemed of interest to attempt a series of transglycosylation reactions in order to form glycosides and nu-

Scheme II



cleosides. When **5** was dissolved in absolute methanol for about 3 hr, what was obtained was not the methyl glycoside, but instead *N*-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)-maleamic acid methyl ester (**6**). Proof of structure was derived from ir and nmr data in addition to elemental analysis. The reaction of **5** with methanol was exceptionally rapid in comparison to other N-substituted maleimides which are reported to undergo slow ring opening in alcohols[14] and some have even been crystallized from alcohols or alcohol-containing solvent mixtures.

When **5** was treated with N^6-benzoyladenine in refluxing nitromethane and the blocking groups were removed with sodium methoxide (Scheme II), adenosine (**11**) was obtained in 44% yield after purification on an ion-exchange column by the method of Dekker.[15] No α anomer was detected although it is known to give a separate peak preceding adenosine.[16] These results indicate that the formation of the orthoacetate ion could be an important part of the process, resulting in exclusive attack by the nucleophile to give only the β anomer. In a similar manner, cytidine (**12**) was prepared in a 25% yield, using N^4-acetylcytosine as the base. A change in solvent, such as to *N*,*N*-dimethylformamide, gave no reaction. The simplicity by which these transglycosylations can be carried out can be somewhat advantageous for synthetic purposes, especially since **5** can be stored for long periods without degradation if kept cold and dry. On the other hand, the nature of the nitrogenous base appears to be very important. Two cytosine derivatives, N^4-benzoylcytosine and N^4-adamantoylcytosine (**13**), and benzimidazole failed to form the desired nucleosides in the reaction mixture.

Experimental Section[17]

2,3,5-Tri-*O*-acetyl-D-ribofuranosyl Chloride (3). To a suspension of tetra-*O*-acetyl-β-D-ribofuranose (14.4 g, 45.3 mmol) in 250 ml of anhydrous ethyl ether was added 1.5 ml of acetic anhydride. The mixture was chilled in an ice bath and dry hydrogen chloride was passed through at such a rate so as to maintain a temperature of 14–18°. When the temperature dropped to 3° and did not rise again, even with vigorous addition of the gas, saturation of the solution was complete and the clear solution was stored in a glass-stoppered flask at 2–3° for 9 days. The solvent was removed by evaporation at 32° and the liquid residue was coevaporated with five 100-ml portions of toluene and then with two 80-ml portions of benzene, leaving a slightly yellow liquid which was used in the following step.

***N*-(2,3,5-Tri-*O*-acetyl-D-ribofuranosyl)maleimide (5).** The entire sample of **3** was dissolved in 400 ml of dry benzene, 9.2 g of silver maleimide[6] was added, and the mixture was stirred at reflux for 5.5 hr. After cooling, the mixture was filtered using a "medium" porosity sintered-glass funnel, and the filtrate was evaporated to dryness. The residue was dissolved in 250 ml of carbon tetrachloride and stored at −19° for 3 days. A small amount of a precipitate was removed by filtration through a "very fine" porosity sintered-glass funnel and the solvent was evaporated (50°), leaving a viscous oil which was dissolved in 800 ml of benzene and washed four times with 800-ml portions of water and dried. Evaporation of the benzene, followed by repeated addition and evaporation of methylene chloride, afforded 13.1 g (81%) of a thick, colorless oil. A portion of this was transformed into a foam by placing it under high vacuum (0.02 mm) for 2 days: $[\alpha]^{25}D$ +121° (*c* 1.93, 1,2-dichloroethane); uv max (1,2-dichloroethane) 278 nm (ϵ 393); ir (film) 3.25 (C=CH), 5.75 (CH_3C=O), 5.81 (NC=O), 8.10 (CO, acetyl), 12.04, 14.45 μ (maleimide ring); nmr ($CDCl_3$) δ 6.60 (s, 2, olefinic H), 6.07 (d, 1, J = 4 Hz, anomeric H), 5.08 (t, 1, J = 4 Hz), 4.8–3.8 (m, 5 H) 2.10 (s, 9, acetyl H).

Anal. Calcd for $C_{15}H_{17}NO_9$: C, 50.71; H, 4.82; N, 3.94. Found: C, 50.33; H, 4.68; N, 3.72.

***N*-(2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl)maleimide (9).** Mercuric maleimide[6] (0.64 g, 1.62 mmol) and 0.4 g of Celite-545 were suspended in 36 ml of dry benzene and traces of moisture were removed by distillation of 12 ml of the solvent. To this mixture was added 0.64 g (1.55 mmol) of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, and refluxing was continued for 48 hr. The cooled reaction mixture was filtered and the filtrate was evaporated. The residue was dissolved in 25 ml of methylene chloride and kept in a refrigerator overnight. A small amount of white precipitate was removed by filtration and the filtrate was washed with 30% aqueous potassium iodide solution (3 × 25 ml). Drying and evaporation of the solvent afforded 0.39 g of a light-amber gum. This was subjected to preparative tlc on two 20 × 20 cm, 2 mm thick F_{254} silica gel plates (E. Merck, Darmstadt) using 1:1 methylene chloride–ethyl ether. The uv absorbing band at R_f 0.48 was excised and extracted from the silica gel with the same solvent mixture, affording 0.21 g (36%) of a white glass following evaporation and high vacuum treatment; uv max (1,2-dichloroethane) 276 nm (ϵ 385); ir (film) 3.23 (-C=CH), 5.72 (C=O), acetyl), 5.83 (NHC=O), 12.08, 14.50 μ (maleimide ring); nmr ($CDCl_3$) δ 6.62 (s, 2, olefinic H), 5.85 (d, 1, J = 4 Hz), anomeric H), 5.20 (t, 1, J = 3 Hz), 5.0-3.6 (series of m, 5), 2.08 (s, 12, acetyl H).

Anal. Calcd for $C_{18}H_{21}NO_{11}$: C, 50.59; H, 4.95; N, 3.28. Found: C, 50.02; H, 5.17; N, 3.26.

Hydrolysis of 5. A small amount (0.42 g, 1.18 mmol) of **5** was shaken in 10 ml of water at 29°. The appearance of maleimide, which is soluble in water, was monitored by gas chromatography on a Hewlett-Packard Model 5700A flame ionization gas chromatograph, equipped with a 20 × ⅛ in. Chromosorb W-AW silicone rubber column. The temperature was 78° and the flow rate of carrier gas (nitrogen) was 27 ml/min. A calibration curve was prepared from known standard concentrations of maleimide in water, and a plot of the amount of maleimide *vs.* peak area was made. Aliquots removed from the aqueous portion of the hydrolysis mixture were injected onto the column and the appearance of maleimide was monitored. Compound **5** appeared to have a half-life of *ca.* 1 hr.

The hydrolysis was also followed qualitatively by tlc using 97:3 benzene–2-propanol and 1:1 methylene chloride–ethyl ether as solvent systems. At the end of 3 hr a homogeneous solution was ob-

tained. The solution was extracted with chloroform and the chloroform was washed with water, dried, and evaporated. Tlc data and the ir spectrum confirmed that the product was 2,3,5-tri-O-acetyl-D-ribofuranose when compared against an authentic sample obtained from hydrolysis of **3**. A sample of maleimide was isolated also and was identical with authentic maleimide, mp 93–95°.

Methanolysis of 5. A mixture of **5** (0.39 g) and anhydrous methanol[18] (10 ml) was stirred for 3.3 hr. The methanol was evaporated, leaving 0.41 g of a light-yellow oil. Tlc in 98:2 chloroform–methanol showed that **5** was absent and a new major compound had formed with several minor components. No free maleimide was detected. The oil was chromatographed on 30 g of silicic acid (Mallinckrodt, 100 mesh) packed in chloroform and 25-ml fractions were collected. Fractions 1–4 were eluted with chloroform, fractions 5–7 with 99:1 chloroform–methanol, and fractions 8–11 with 98:2 chloroform–methanol. The product was eluted in fraction 11. Evaporation of the solvents gave 0.21 g of **6** which was homogeneous by tlc. Coevaporation with ethyl ether caused the syrup to form a hard, glass-like foam, which was dried at 0.02 mm for 2 days: uv max (1,2-dichloroethane) 229 nm (ε 5,300); ir (film) 3.05 (NH), 5.75 (CH_3C=O), 5.82 (MeO-C=O), 6.12 (–NH-C(=O)– or –C=CC(=O)–), 6.5 μ (amide II); nmr ($CDCl_3$) δ 6.13 (m, 2, olefinic H),[19a] 6.02 (d, 1, J = 3 Hz anomeric H), 5.10 (t, 1, J = 4 Hz), 4.8–4.0 (series of m, 4 H), 3.76 (s, 3, OCH_3), 2.07, 2.05 (both s, 6, acetyl H), 1.83 (s, 3, acetyl H),[19b] 9.33 (s, 1, –NHCO).

Anal. Calcd for $C_{16}H_{21}NO_{10}$: C, 49.61; H, 5.46; N, 3.62. Found: C, 49.67; H, 5.45; N, 3.65.

Transribosylation. A. Preparation of Adenosine (11). A mixture of **5** (1.39 g) and N^6-benzoyladenine (0.96 g) in 90 ml of freshly distilled, dry nitromethane was heated at reflux for 17 hr. The orange-colored solution was evaporated, the residue was triturated with chloroform, and some unreacted N^6-benzoyladenine (0.22 g) was removed by filtration. Evaporation of the solvent gave 2.36 g of a thick syrup which was dissolved in 300 ml of methanol, 10 ml of 1N methanolic sodium methoxide was added, and the mixture was refluxed for 2 hr. The methanol was evaporated, the residue was dissolved in 250 ml of water, and the pH was adjusted to 6.4 with Bio-Rad AG50W-X8 (H^+) resin. The resin was removed by filtration and washed with water. The water was evaporated and the resulting syrup (1.53 g) was dissolved in 15 ml of water and applied to the top of a column (45 × 1.8 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh), packed in water. The column was eluted with 15% aqueous methanol and 20-ml fractions were collected.[15] The eluate was monitored at 254 nm and at fraction 120, the solvent was changed to 30% aqueous methanol. Tubes 165–280, which absorbed in the uv, were pooled and the solvents evaporated. Crystallization from water afforded adenosine (**11**), 0.46 g (44%), mp 239–241°. Admixture of an authentic sample of commercial adenosine (also recrystallized from water) gave no depression of melting point. The ir and nmr spectra were identical, as were the chromatographic mobilities by tlc (solvents: water; 86:14 1-butanol–water, v/v) and paper chromatography (solvents: 5% aqueous disodium hydrogen phosphate and 4:1:5 1-butanol–acetic acid–water, v/v, top layer).

B. Preparation of Cytidine (12). A mixture of 0.27 g (0.7 mmol) of **5** and 0.108 g of N^4-acetylcytosine in 15 ml of nitromethane was heated at reflux for 24 hr. Some unreacted N^4-acetylcytosine (51 mg) was filtered off when the mixture had cooled. Evaporation gave a thick syrup, which was dissolved in 7 ml of chloroform and some additional N^4-acetylcytosine was again removed by filtration. The solvent was evaporated, and the syrup was dissolved in 30 ml of methanol and treated with 1 ml of 1N methanolic sodium methoxide and kept at room temperature for 24 hr. The work-up was the same as for adenosine, except that the column (15 × 2 cm) was eluted with 20% aqueous methanol and 7-ml fractions were collected. Tubes 32–64, which contained the product, were pooled and evaporated. Cytidine (**12**) was crystallized from 8 ml of ethanol containing several drops of water, 40 mg (25%), mp 219–220°. Admixture with an authentic sample of commercial cytidine (also recrystallized from aqueous ethanol) gave no depression of melting point. The uv and ir spectra were identical, and chromatographic mobility by tlc and paper chromatography are the same.

***N*-Trimethylsilylmaleimide (10).** A mixture containing 9.7 g (0.10 mol) of maleimide, 31 ml (d 0.845 g ml^{-1}) of trimethylsilyl chloride, 34 ml of triethylamine,[20] and 300 ml of dry benzene was stirred at reflux for 24 hr under a nitrogen atmosphere. The reaction mixture was concentrated to 200 ml by distillation and triethylammonium chloride was removed by filtration after the mixture had cooled. The solvent was evaporated and the oil was distilled through a Vigreaux column at 55 mm. The product **10** was obtained as a clear, colorless oil, 12.4 g (71%): bp 118–122°, uv max (1,2-dichloroethane) 281 nm (ε 484); ir (CCl_4) 3.30 (C=CH), 5.85 (C=O), 14.27 μ (maleimide ring); nmr (CCl_4) δ 6.55 (s, 2. olefinic H), 0.27 (s, 9, methyl H).

Anal. Calcd for $C_7H_{11}NO_2Si$: C, 49.68; H, 6.55; N, 8.28. Found: C, 49.57; H, 6.59; N, 8.52.

N-Trimethylsilylmaleimide was quite stable for many months when stored in a desiccator. Upon contact with water, maleimide (**7**) was immediately generated.

***N*⁴-Adamantoylcytosine (13).** Adamantoyl chloride (4.21 g, 21 mmol) was slowly added to a stirring suspension of cytosine (1.17 g, 11 mmol) in 100 ml of dry pyridine. The mixture was heated in oil bath to 78° and kept at this temperature for 3 hr. The clear solution was poured into 120 ml of ice–water, whereupon a gum separated. Chloroform (400 ml) was added and the mixture was stirred and chilled in an ice bath while 420 ml of 3N hydrochloric acid was slowly added, dropwise. The temperature was maintained below 15° throughout this operation. The chloroform layer was separated and washed with water (250 ml) and 5% aqueous sodium bicarbonate (300 ml) and dried. Evaporation of the solvent afforded a white solid which was tritruated with 40 ml of chloroform. Filtration gave 1.89 g and an additional 0.24 g was obtained by two similar treatments of the filtrate using *ca.* 15 ml of chloroform each time. The combined product was crystallized from 300 ml of absolute ethanol, 1.16 g of shiny platelets. A second crop, 0.16 g (total yield, 43%), was obtained, mp 347–350° dec: uv max (absolute ethanol) 245 (ε 16,940), 296 nm (ε 6,410), identical with N^4-acetylcytosine;[21] ir (KBr) 3.00, 3.08, 3.46, 5.86, 5.91, 5.96, 6.17, 6.35, 6.40 μ; nmr (trifluoroacetic acid) δ 10.10 (s, 1, –NHCO), 8.35 (d, 1, J = 7 Hz, C-5 H), 6.82 (d, 1, J = 7 Hz, C-6 H), 2.06, 1.86 (adamantane ring protons).

Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.81; H, 7.01; N, 15.37. Found: C, 65.60; H, 7.18; N, 15.07.

Registry No.—**3,** 40554-98-1; **5,** 53209-76-0; **6,** 53209-77-1; **9,** 53209-78-2; **10,** 53209-79-3; **11,** 58-61-7; **12,** 65-46-3; **13,** 53209-80-6; tetra-O-acetyl-β-D-ribofuranose, 13035-61-5; 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide, 572-09-8; N^6-benzoyladenine, 4005-49-6; N^4-acetylcytosine, 14631-20-0; maleimide, 541-59-3.

References and Notes

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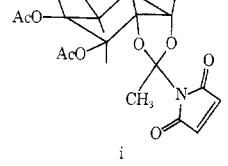
(12) One of the referees suggested that this could occur *via* an ortho imide intermediate (i), which could form the O-glycoside in the α configuration. This in turn could undergo an O → N rearrangement to give **9.** Such intermediates and rearrangements have been previously proposed; *e.g.*, R. U. Lemieux and A. R. Morgan, *Can. J. Chem.*, **43,** 2214 (1965); K. A. Watanabe, D. Hollenberg, and S. S. Fox, *J. Carbohyd. Nucleosides, Nucleotides,* **1,** 1 (1974). Another possibility is prior formation



i

of the β-O-glycoside which is anomerized to the α-O-gylcoside under the influence of mercuric bromide. This could then rearrange to the N-substituted compound **9**. For an example, see G. Wagner and H. Frenzel, *Arch. Pharm.* (*Weinheim*), **299**, 536 (1966).

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(17) Melting points were determined on a Kofler micro hot stage and are corrected values. Nmr spectra were determined on a Varian T-60A spectrometer using TMS as the internal reference. Ir spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer and uv spectra were obtained on a Beckman DK-2 spectrophotometer. Elemental analyses were performed by the Baron Consulting Co., Orange, Conn., or the Spang Microanalytical Laboratory, Ann Arbor, Mich. Moist organic solutions were dried over anhydrous magnesium sulfate. Evaporations were carried out on a rotary evaporator under reduced pressure and a bath temperature of about 40°, except where noted otherwise. Tlc was performed on precoated silica gel F-254 plates (E. Merck, Darmstadt) of 0.25 mm thickness. Spots were first located with an ultraviolet lamp and the plates were then sprayed with a solution of 20% ethanolic sulfuric acid and heated in an oven at 140°.
(18) Reagent grade methanol was percolated through a column of molecular sieve 3A and stored over calcium hydride. Distillation under nitrogen through a column of Raschig rings gave anhydrous methanol which was stored over molecular sieve 3A.
(19) (a) It was expected that the olefinic protons would produce a typical AB quartet. When this region was swept over a 50 Hz width, some separation into two very broad peaks was accomplished. (b) Molecular models showed that the acetyl groups at C-2′ or C-5′ can interact with the double bond and, therefore, be influenced by an anisotropic effect, which probably accounts for the shift in one of the methyl peaks.
(20) Triethylamine was purified by distillation from phenylisocyanate just prior to use.
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Crystal and Molecular Structure of β-Peltatin A Methyl Ether

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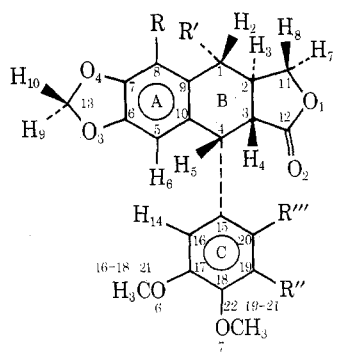
The crystal structure of β-peltatin A methyl ether ($C_{23}H_{24}O_8$), a natural antitumor agent, has been solved by direct methods with the aid of the combined figure of merit. The space group is $C222_1$. Cell dimensions are a = 23.670, b = 10.024, c = 17.611 Å, and Z = 8. The structure was refined to R = 0.046. The conformation is similar to that of the 5′-demethoxy compound except for the methoxyl groups, which are all rotated differently in the two compounds. Presumably the favored conformation of other antitumor lignans is similar except for methoxyl rotation.

β-Peltatin A methyl ether (I) and 5′-demethoxy-β-peltatin A methyl ether (II), both isolated from the Mexican plant *Bursera fagaroides* (Burseraceae),[1] are antitumor agents of the podophyllotoxin (III) class. An X-ray study on II[2] revealed its conformation in the crystalline state. We have now completed an X-ray study of the former, which shows some aspects of the conformations of the two substances to be similar and some different. This is the second X-ray study of an antitumor lignan; in addition, a derivative, 2′-bromopodophyllotoxin (IV), was recently studied[3] to check the absolute configuration of the compounds of this series.



	R	R′	R″	R‴
I	$O^5C^{14}H_3^{11-13}$	H^1	$O^6C^{23}H_3^{22-24}$	H^{15}
II	OCH_3	H	H	H
III	H	OH	OCH_3	H
IV	H	OH	OCH_3	Br

Experimental Section

Collection and Reduction of the Data. Oscillation and Weissenberg photographs of a needle 0.2 × 0.2 × 0.4 mm indicated space group $C222_1$. The cell parameters were found by least-squares fitting of the settings for the four angles of eight reflections on a Picker-FACS-I diffractometer (Cu Kα, λ = 1.54178 Å, graphite monochromator) to be a = 23.670 (9), b = 10.024 (4), c = 17.611 (8) Å, ρ_{calcd} = 1.37, ρ_{obsd} = 1.40 g/ml, and Z = 8. Intensity data were collected using a scintillation counter with pulse-height analyzer, θ–2θ scan technique, 2°/min scan rate, 10-sec background counts, attenuators when the count rate exceeded 10^4 counts/sec, and 2° scan range with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 1889 independent reflections measured, $1630 > 3\sigma(I)$ were considered observed. Three standard reflections were monitored every 50 measurements; no decrease in the intensity of the standards was observed. Lorentz and polarization corrections were applied to the data, but no correction was made for absorption.

Solution and Refinement. The structure was solved by direct methods using the MULTAN[4] program with 308 E's > 1.4. The correct solution had the highest *combined* figure of merit (C), defined as

$$C = \frac{\Sigma\alpha - \Sigma\alpha_{min}}{\Sigma\alpha_{max} - \Sigma\alpha_{min}} + \frac{(\psi_0)_{max} - \psi_0}{(\psi_0)_{max} - (\psi_0)_{min}} + \frac{R_{max} - R}{R_{max} - R_{min}}$$

where $\Sigma\alpha$ (absolute figure of merit), ψ_0, and R are the usual three indicators employed in the program. The correct solution was 11th in $\Sigma\alpha$, 27th in ψ_0, and 5th in Resid. All the nonhydrogen atoms were located from the E map. Two cycles of full matrix isotropic least-squares refinement of nonhydrogen atoms reduced R to 0.145, and then two anisotropic cycles to 0.094. A difference Fourier map showed all the hydrogens except H-16–H-18, whose positions were calculated. One more cycle of least-squares refinement in which nonhydrogen atoms were refined anisotropically and hydrogen atoms isotropically reduced R to 0.046. Refinement was terminated at this stage since the average ratio of shifts in parameters to standard deviations was less than 0.3. Unit weights were used and refinement was based on F_o with $\Sigma(F_o - F_c)^2$ minimized. The scattering factors used were those of Hanson, *et al.*[5] No correction was applied for extinction.