Anal. Calcd for $C_{23}H_{27}O_7Cl$: C, 61.26; H, 6.04. Found: C, 61.12; H, 5.97.

Registry No.—**2a**, 57015-41-5; **2b**, 57015-42-6; **4a**, 57015-43-7; **4b**, 57015-44-8; **7a**, 57015-45-9; **8a**, 57015-46-0; **9a**, 57015-47-1; **9b**, 57015-48-2; **10a**, 57015-49-3; **10b**, 57015-50-6; **11a**, 57015-51-7; **11b**, 57015-52-8; **12a**, 57015-53-9; **15a**, 57015-54-0; **15b**, 57015-55-1; **16a**, 57015-56-2; **16b**, 57015-57-3; **19a**, 57015-58-4; **19b**, 57015-59-5; **20a**, 57015-60-8; **20b**, 57015-61-9; **21**, 57015-62-0; **22**, 57015-63-1; **23**, 57015-64-2; **24**, 57015-65-3; **25a**, 57015-66-4; **26a**, 57031-28-4; **27a**, 57015-67-5; **27b**, 57015-68-6; **28a**, 57015-69-7; **28b**, 57015-70-0; **29a**, 57015-71-1; **30a**, 57015-72-2; **31**, 57015-73-3; **32**, 57015-74-4; **33**, 57015-75-5; **35**, 36623-21-9; **36a**, 57015-76-6; phosgene, 75-44-5.

References and Notes

(1) This research was supported wholly by a grant, AM 01255, from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U.S. Public Health Service. We are grateful to this Institute for its continued and generous support of our work.
(2) Address correspondence to Department of Medicine, Crozer-Chester Medical Center, Chester, Pa. 19013.
(3) M. L. Lewbart, *J. Org. Chem.*, **38**, 2328 (1973).
(4) The preparation of this previously undescribed monoketal was made possible by our observation that the presence of a 17α-acetoxy group prevents ketalization at C-20. Thus treatment of 17α-acetoxypregn-4-ene-3,20-dione (5.0 g) in benzene (250 ml) and ethylene glycol (40 ml) with *p*-TSA (150 mg) for 8 hr by the Bernstein procedure gave 5.2 g (93%) of leaflets from ethyl acetate: mp 230–233°; $[\alpha]D$ −17.4°. Reported[5] for **17-acetoxypregn-5-ene-3,20-dione 3-ethylene ketal:** mp 241–243°; $[\alpha]D$ −62° (chloroform). Saponification of the acetoxy ketal (4.16 g) in a mixture of methylene chloride (100 ml) and methanol (250 ml) with aqueous 1 *N* sodium hydroxide (50 ml) was carried out for 2 hr on a steam bath. The product crystallized spontaneously from the concentrated solution. Recrystallization of the crude material from ethyl acetate afforded **17-hydroxypregn-5-ene-3,20-dione 3-ethylene ketal** as leaflets in a total yield of 2.54 g (68%): mp 244–246°; $[\alpha]D$ −58.9°; ν_{max} 3490 (hydroxyl), 1705 (sh), 1695 (20-ketone), 1100 cm^{-1} (ketal). Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.91; H, 9.26. Deketalization of the saponification product in acetone–*p*-TSA gave a product identical in all respects with **17-hydroxyprogesterone.**
(5) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson, and J. A. Campbell, *Chem. Ind. (London)*, 1002 (1958).
(6) As far as we are aware the monoketal **6** has not been described previously. The reaction sequence, as in the preparation of the 11-deoxy analogue **5**, follows. Forced acetylation of 21-deoxycortisone (3.0 g) in acetic acid (120 ml) and acetic anhydride (24 ml) in the presence of *p*-TSA (2.4 g) was carried out for 1.25 hr at room temperature. The crude product, recovered in the usual manner, was chromatographed on a silica gel column. Crystallization of the mobile component from methanol gave 800 mg (21%) of **3,17-diacetoxypregna-3,5-diene-11,20-dione** as prisms: mp 163–165°; $[\alpha]D$ −79.5°; λ_{max} 234 nm (ϵ 19500); ν_{max} 1735, 1250, and 1220 (acetate), 1706 (11- and 20-ketone), 1671 and 1638 cm^{-1} ($\Delta^{3,5}$). Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53; CH_3CO, 20.09. Found: C, 69.90; H, 7.64; CH_3CO, 19.45. Crystallization of the major, polar fraction from methanol furnished 2.0 g (59%) of **17-acetoxypregn-4-ene-3,11,20-trione** as platelets: mp 205–207°; $[\alpha]D$ 143°; λ_{max} 238 nm (ϵ 16100); ν_{max} 1733 and 1255 (acetate), 1710 cm^{-1} (11- and 20-ketone). Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; CH_3CO, 11.14. Found: C, 71.38; H, 7.86; CH_3CO, 10.70. Ketalization of the 17-acetate by the Bernstein procedure afforded **17-acetoxypregn-5-ene-3,11,20-trione 3-ethylene ketal** (75% yield) in the form of prisms from ethyl acetate: mp 207–211°; $[\alpha]D$ 0.85°; ν_{max} 1733 and 1255 (acetate), 1705 (11- and 20-ketone), 1100 cm^{-1} (ketal). Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.64; H, 7.96. Saponification of the acetoxy ketal as in the preparation of the 11-deoxy analogue afforded in 41% yield **17-hydroxypregn-5-ene-3,11,20-trione 3-ethylene ketal (6)** as prisms from ethyl acetate: mp 208–212°; $[\alpha]D$ −41.4°; ν_{max} 3460 (hydroxyl), 1705 (11- and 20-ketone), 1098 cm^{-1} (ketal). Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.88; H, 8.34.
(7) M. L. Lewbart, *J. Org. Chem.*, **38**, 2335 (1973).
(8) N. S. Bhacca and D. H. Williams, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, p 57.
(9) The author is deeply indebted to Dr. Byron Arison of the Merck Institute for the determination and interpretation of all NMR spectra included in this paper.
(10) M. L. Lewbart, *J. Org. Chem.*, **37**, 3892 (1972).
(11) M. L. Lewbart, *J. Org. Chem.*, **37**, 1233 (1972).

Nucleosides. XCIV. Synthesis of Some C Nucleosides by 1,3-Dipolar Cycloadditions to 3-(Ribofuranosyl) Propiolates[1]

Federico G. De Las Heras, Steve Y-K. Tam, Robert S. Klein, and Jack J. Fox*

Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, Sloan-Kettering Division of Graduate School of Medical Sciences, Cornell University, New York, New York 10021

Received July 18, 1975

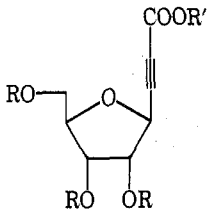
Condensation of 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl chloride (**3**) with the silver acetylide of methyl (or ethyl) propiolate **4a** (or **4b**) gives fair yields of the β-D-ribofuranosyl propiolate **5a** (or **5b**). 1,3-Dipolar cycloaddition of **5a** with trimethylsilyl azide gives directly the deblocked 1,2,3-triazole ester **7** which on treatment with methanolic ammonia affords amide **8**. 1,3-Dipolar cycloaddition of **5a** (or **5b**) with diazomethane gives the fully blocked 4-ribosylated pyrazole ester **9a** (or **9b**) in good yields along with the *N*-methyl derivative **10a** (or **10b**). Compound **9a** (or **9b**) can be readily deblocked to the corresponding 4-ribosylpyrazole ester **13a** (or **13b**) or treated with ammonia to give the blocked pyrazole amide **11**. A similar cycloaddition reaction of **5a** with ethyl diazoacetate (**15**) affords the 4-ribofuranosylpyrazole-3,5-dicarboxylate **16** as the major product and some 3-ribofuranosylpyrazole-4,5-dicarboxylate **17**. These two products have been unequivocally identified by comparing them with the products (**16** and **19**) obtained from the cycloaddition reaction of **5b** with methyl diazoacetate (**18**).

A relatively new group of naturally occurring nucleosides[2] exhibiting important biological activities has been isolated recently. They are the C-nucleoside antibiotics formycin, formycin B, showdomycin, and pyrazomycin. Also belonging to this class of compounds is the most recently isolated oxazinomycin,[3] a close analogue of pseudouridine.[4] All, except pseudouridine, possess antibiotic properties and many exhibit anticancer and antiviral activities. These biological properties, together with their unique structural feature (a C–C linkage between the heterocycle and the sugar), have elicited many efforts directed toward the synthesis of such compounds or analogues thereof.

The methods described for the synthesis of C nucleosides can be classified into three general types. The first involves the conversion of some available C nucleosides to prepare new ones. 6-Azapseudouridine, for example, has been synthesized[5] from pseudouridine. Oxazinomycin has been converted to pseudouridine[3c] and formycin has been obtained from formycin B.[6] The second approach, direct condensation of suitably blocked sugar derivatives with appropriate heterocyclic bases (usually as metalated derivatives), has been utilized for the preparation of pseudouridine[7] or some of its sugar analogues,[8] 5-ribosylcytosine[9] and 1-deazauridine.[10] The third and most fruitful approach to date has been the multistep elaboration of the desired heterocycle

from a *C*-glycosyl derivative functionalized at the $C_{1'}$ substituent. By this general method showdomycin,[11] formycin B,[12] oxoformycin,[13] and pyrazomycin[14] were prepared. One type of *C*-glycosyl derivative which has received much attention recently is represented by the *C*-glycosyl acetylenes,[15-20] some of which have been utilized to prepare simple triazole,[15a,18] pyrazole,[20] and isoxazole[19] C nucleosides via 1,3-dipolar cycloaddition reactions to the triple bond.[21]

Synthesis of Ribofuranosyl Acetylenic Esters. We have investigated the synthesis of ribosyl acetylenic derivatives such as **1** because (1) acetylenic esters are more reac-



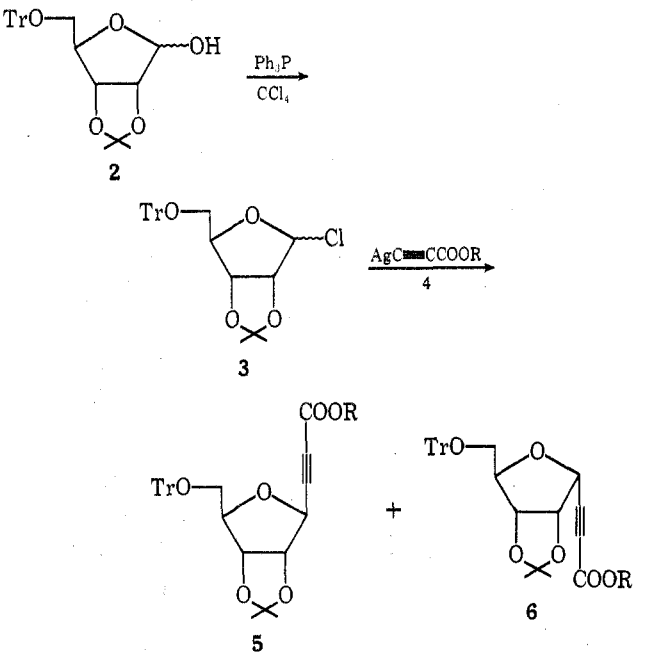
1

tive to 1,3-dipolar cycloaddition reactions than ordinary alkynes[21] and (2) they can also be used as intermediates for the elaboration of six-membered heterocycles via reaction of the two electrophilic sites (acyl function and β carbon) with reagents containing the amidino or ureido function,[22] or for the synthesis of five-membered heterocycles with reagents such as hydrazine[23] or hydroxylamine.[24]

Most methods described to prepare glycosyl acetylenes have used the reaction of a suitably blocked sugar[15,17] or a glycosyl halide[16,20] with an acetylene Grignard reagent[25] and therefore such methods were not immediately applicable to the synthesis of the ester **1**. As an alternate approach, the reaction of a suitably protected halogenose with the silver acetylide of an alkyl propiolate[26] was considered. The potential utility of readily available halogenoses such as the tri-*O*-acyl D-ribofuranosyl halides seemed doubtful in view of the known propensity of sugar halides bearing participating acyl groups at C-2 to give 1,2-ketal derivatives upon reaction with organometallic compounds.[10,27,28] This view was recently confirmed by a report from Albrecht, Repke, and Moffatt,[29] who have obtained 3,5-di-*O*-benzoyl-1,2-*O*-[α-(2-carbomethoxyethynyl)benzylidene]-α-D-ribofuranose as a major product of the reaction of tri-*O*-benzoyl-D-ribofuranosyl bromide with the silver derivative of methyl propiolate. The recently synthesized 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride (**3**),[30] on the other hand, appeared to be a promising candidate for this type of reaction.

Condensation of the silver acetylide of ethyl propiolate (**4b**, Chart I) with the crystalline 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride (β anomer of **3**) afforded an "anomeric"[31a] mixture of ethyl 3-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)propiolates (**5b** and **6b**).[31b,32] After ready separation by dry column chromatography, the faster moving β anomer **5b** was isolated as a syrup while the slower moving α anomer was obtained in crystalline form (**5b**/**6b** ~ 3, by weight). The assignment of anomeric configurations was based on the following ^{1}H NMR data: (a) The chemical shift of H-1′ for **5b** is smaller (δ 4.76) than that for **6b** (δ 5.18). This consistent relationship between the chemical shift of H-1′ of a pair of anomers has been utilized previously to assign the configuration at C-1′ to nucleosides[33] and C glycosides.[34] (b) The $J_{1',2'}$ value in **5b** is smaller (2.8 Hz) than that in **6b** (4.7 Hz). Although not conclusive, the difference in coupling constants for these two fairly rigid 2,3-*O*-isopropylidenated ribofuranosyl systems supports the assignments made. (c) The ^{1}H NMR spectra of *all* C nucleosides (**9b, 10b, 11, 16,** and **19**) derived from **5b** (vide infra) exhibit differences between the chemical shifts of the isopropylidene methyl signals ($\Delta\delta$ 0.23–0.30) in excellent agreement with the values characteristic of β nucleosides.[35]

Chart I



For compounds **4**, **5**, and **6**: a, R = Me; b, R = Et

This condensation reaction (**3** → **5** + **6**) is affected by several factors. (a) For optimum yields, the silver acetylide must be dried in vacuo (pump) at room temperature[36] for at least 2 days. (b) Condensation rates are dependent on the solvent used. Under comparable reagent concentrations, a reaction would be completed, for example, in 3 hr in dichloromethane whereas in benzene, 2 weeks are required. In both cases, however, the ratio of β (**5b**) to α (**6b**) anomers was fairly constant (~3:1) with a total yield of 55–60%. (c) It was found that if conditions were not kept scrupulously free of protic impurities, the amount of various side products, that are always formed to some extent, increased appreciably. Some of the side products which have been isolated by chromatography were identified by ^{1}H NMR spectroscopy as 1,5-anhydro-2,3-*O*-isopropylidene-β-D-ribofuranose, ethyl 3-trityl propiolate, and compound **2**.

In order to avoid the fairly elaborate work-up which accompanies the isolation of crystalline ribofuranosyl chloride **3**[30b] and the unavoidable partial loss of material, conditions were sought which would permit preparation of **3** and its condensation in situ with **4b** to give **5b** (Chart I) in a "one pot" reaction. Of particular importance was the desirability of a solvent suitable for both reactions (**2** → **3** → **5** + **6**) since DMF, the solvent originally used in the preparation of the ribosyl chloride **3**,[30] was found to be totally inadequate for the condensation step, giving mostly products resulting from undesirable reactions. The reasons for this are not yet clear. It was found that acetonitrile is a suitable solvent for the preparation of **3** and its condensation in situ with **4b**. This method has afforded reproducible yields (45% from **2**) of a mixture of the β (**5b**) and α (**6b**) anomers in a ratio of ~5:1. Slightly lower yields have been obtained when dichloromethane was used as the solvent.

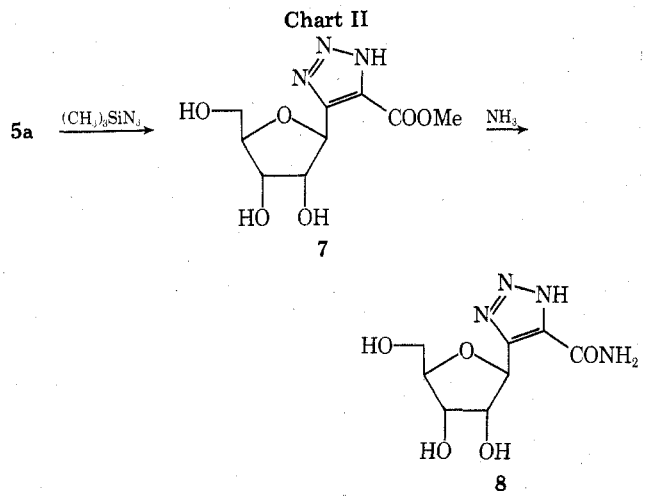
A similar procedure for the in situ condensation of **3** with the silver acetylide of methyl propiolate **4a** in acetonitrile or dichloromethane has yielded results comparable to those described above for the ethyl derivatives.

It has been shown also that reaction of **2** with triphenylphosphine and carbon tetrachloride gives the β anomer of the chloro sugar **3** via an intermediate. Thus TLC monitoring of the reaction of **2** with triphenylphosphine and carbon tetrachloride in acetonitrile or dichloromethane revealed the initial formation of an intermediate compound (R_f ~0.45 *in petroleum ether–ethyl acetate, 10:1) which is* slowly but completely converted to the known 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride (the β anomer of **3**) (R_f ~0.6 in petroleum ether–ethyl acetate, 10:1). Since the starting material **2** is a mixture of anomers with the β anomer predominating[30] and since this type of reaction generally proceeds by inversion of configuration,[37] it is reasonable to assume that the initially formed product is the α-ribosyl chloride which in the presence of chloride ion epimerizes to the more stable β-chloro anomer. This hypothesis is supported by monitoring the reaction of **2** with triphenylphosphine and carbon tetrachloride in $CDCl_3$ simultaneously by ^1H NMR[38] and TLC. As the signals for the β anomer of **2** (H-1, δ 5.30, $J_{1,2}$ = 0 Hz) decrease in intensity, a new set of signals, attributable to the intermediate described above, appears which includes a doublet at low field (δ 6.30 $J_{1,2}$ = 6.2 Hz). As the reaction proceeds, the signals of **2** slowly disappear while signals corresponding to the known β-chloro anomer of **3** (H-1, δ 6.09, $J_{1,2}$ = 0 Hz) increase in intensity. The relative values of the chemical shifts and coupling constants of the low-field doublet (δ 6.30) and of the H-1 signal of the β anomer of **3** are consistent with the expected parameters of the anomeric pair of **3**. Analogous results have been obtained by following the course of the reaction in CD_3CN by ^1H NMR spectroscopy.

1,3-Dipolar Cycloaddition Reactions of 5a and 5b. Among the various 1,3-dipolar cycloaddition reactions that alkynes undergo readily, the reaction with azides has been found of synthetic value for the preparation of 1,2,3-triazoles.[39] The use of trimethylsilyl azide is of particular interest since this reagent is stable and can be used in place of the explosive hydrazoic acid for the synthesis of N-unsubstituted triazoles (the Si–N bond being easily cleaved by protic solvents).[40]

Treatment of the methyl ester **5a** (Chart II) with 5–6 equiv of trimethylsilyl azide at 105°C for 20 hr in a sealed

Chart II

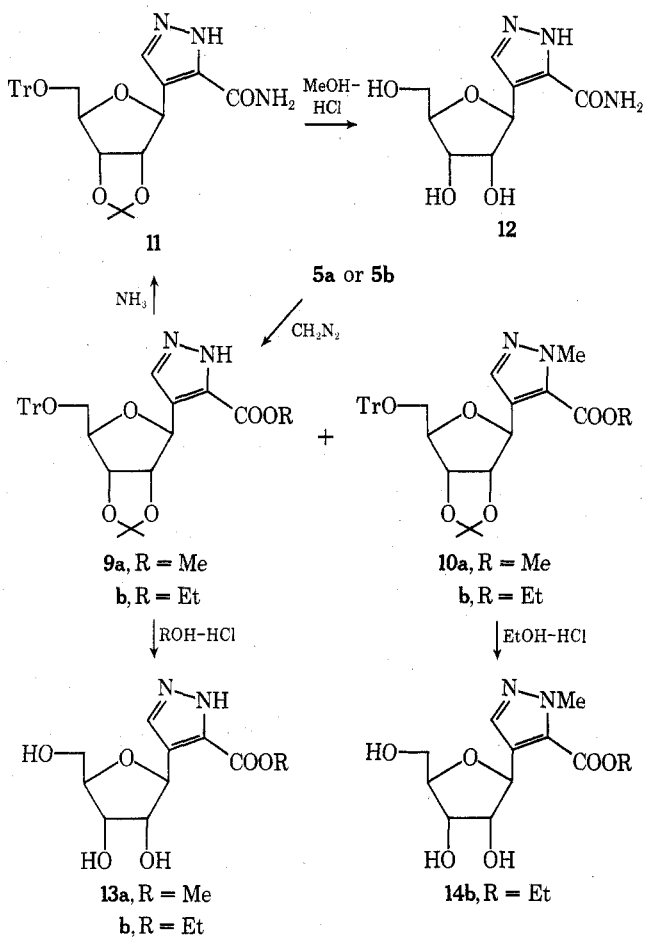


vessel was sufficient for complete conversion of the acetylenic function to the triazole. This major reaction, however, was accompanied by partial removal of the trityl and isopropylidene functions, leading to a mixture of partially blocked derivatives of 5(4)-carbomethoxy-4(5)-(β-D-ribofuranosyl)-1,2,3-triazole (**7**). These side reactions may have been catalyzed by the formation of some hydrazoic acid during the reaction. Extending the reaction time had no adverse effect, however, on the stability of the already formed triazole ring while allowing complete removal of all blocking groups from the ribose moiety. This procedure has afforded directly the desired crystalline triazole **7** from **5a** *in good yield. Conversion of the ester* **7** *to the amide* **8** was accomplished in good yield on treatment of **7** with 50% NH_3 in methanol for 3 days at 60°C in a sealed vessel.

Another type of 1,3-dipolar cycloaddition to acetylenes is their reaction with diazoalkanes to afford pyrazoles.[23] In view of the biological importance of the formycins and pyrazomycins which contain a pyrazole ring ribosylated at position 3(5), it was of interest to determine the utility of esters **5a** and **5b** as intermediates for the synthesis of pyrazole C nucleosides by reaction with diazoalkanes.

Reaction of **5a** with a slight excess of diazomethane (Chart III) in ether at 0°C was completed within 30–45

Chart III



min. Two products detected by TLC were isolated by column chromatography. The major component, obtained in 72% yield, was identified as the pyrazole ester **9a.** The minor component, obtained in 3.5% yield, was found to be a *N*-methyl derivative formed by the secondary reaction of **9a** with an excess of diazomethane. Similarly, reaction of **5b** with diazomethane gave **9b** (72%) and **10b** (10%).

The minor products were tentatively assigned structure **10** by analogy with many studies on alkylation in the pyrazole series.[41] These have led to the generalization that pyrazoles substituted by an electron-withdrawing group (such as acyl) at the 3 or 5 positions usually undergo alkylation mainly, *if not exclusively, at the adjacent nitrogen atom.* Although these results may vary depending on the condi-

tions of alkylation, the rule seems to have no exception when diazomethane is employed as the alkylating agent.

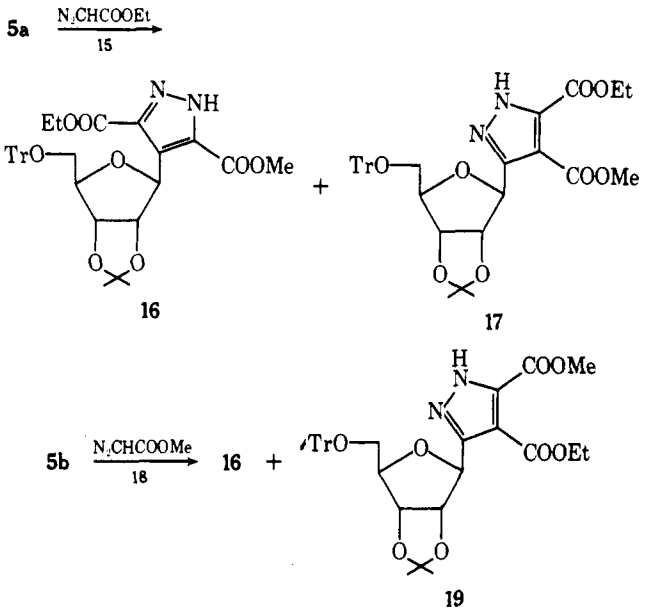
Treatment of **9a** or **9b** with ammonia–methanol (50%) at 50–75° for 3–4 days afforded good yields of the crystalline amide **11**. Removal of the protecting groups with methanolic HCl afforded a good yield of the known crystalline amide **12**.[29,42] Similar deblocking reactions of **9b** and **9a** with methanolic HCl afforded **13b** and the known **13a**,[29] both as crystalline materials. Treatment of the minor product **10b** with MeOH–HCl gave the unblocked N-methylated derivative **14b** in crystalline form.

The foregoing reactions of the acetylenic esters **5a** and **5b** with diazomethane afforded as expected the pyrazole esters ribosylated at position 4 as the only detectable product. These results are consistent with previous studies[21,23,43] on the mechanism and mode of addition of diazoalkanes to activated dipolarophiles. According to these studies the terminal nitrogen of the diazo compound attaches to the carbon α to the activating electron-withdrawing group (COOR). Our results also parallel recent observations by Albrecht, Repke, and Moffatt,[29] who found no positive evidence for the inverse mode of cycloaddition of diazomethane or diazo esters to a blocked derivative of the acrylate analogue of **5a**. The products of such inverse addition are desirable since they possess the common structural feature present in pyrazomycin and formycin, namely a 3(5)-ribosyl pyrazole.

Since there are numerous reports showing that inverse 1,3-dipolar addition of diazoalkanes occur more readily to substituted acetylenic dipolarophiles than to the corresponding analogously substituted ethylenic derivatives,[21b,43c,d,44,45] further investigation of the cycloaddition reactions of **5a** and **5b** with other diazoalkanes was undertaken. Diazo esters are particularly suitable for such a study for the following reasons. It has been reported, for example, that while diazomethane adds to $C_6H_5C{\equiv}C$–COOEt to give equal amounts of the products formed by "normal" and "inverse" mode of addition, the reaction with methyl diazoacetate gives chiefly the product derived from "inverse" addition.[44] Furthermore, should inverse addition occur with **5a** or **5b** the products obtained (such as **17** and **19**) would be directly suitable for the synthesis of formycins or formycin analogues.[12,13]

Reaction of the methyl propiolate derivative **5a** with an excess of ethyl diazoacetate (**15**, Chart IV) afforded two products of different chromatographic mobilities on silica thin layer. The major product (slower moving) was obtained in 63% yield after crystallization from the reaction mixture and subsequent chromatography of the mother liquors, while the minor component could be isolated in 10% yield by chromatography. Uv and ^{1}H NMR spectroscopic data indicated that the two components were indeed the expected pyrazole derivatives **16** and **17**, each formed by one of the two possible modes of cycloaddition. It was not possible, however, to assign these products a definite structure (such as **16** or **17**) since their physical properties (uv, ir, ^{1}H NMR) could fit either one. Chemical proof of their structures was obtained as follows. After treatment of the ethyl propiolate derivative **5b** with methyl diazoacetate (**18**) at room temperature for 9 days, two products of different mobility could be detected by TLC. The major slower moving component obtained in 56% yield by crystallization directly from the reaction mixture and subsequent column chromatography of the mother liquor was found to be identical in all respects with the major product **16** obtained from the previous reaction. This common product only could arise from the "normal" mode of addition and has, therefore, structure **16**. The minor product (8% after chromatography), as expected, was found to be different from all other products, as deduced from its melting point, ir, and ^{1}H NMR spectra, and its behavior on TLC. It was therefore assigned structure **19**. It also follows that the minor component obtained from the previous reaction of **5a** with **15** has structure **17**. In view of the synthetic significance of compounds **17** and **19** as potential intermediates for the synthesis of formycin analogues, the 1,3-dipolar cycloaddition reactions of **5a** and **5b** with the diazo esters described above were repeated at higher temperature, since a decrease in the stereoselectivity of the reaction should result in a corresponding increase in the relative yield of the desired minor products. Such modifications in the original conditions resulted in appreciable increases in the yields of **17** and **19**. Thus, reaction of **5a** with **15** at 50°C for 20 hr afforded 61% of **16** and 15% of **17** and reaction of **5b** with **18** at 50°C for 2 days afforded 54% of **16** and 13% of **19**.

Chart IV



The present method which readily provides pyrazole dicarboxylic acid derivatives such as **17** and **19** in essentially two steps from the readily available blocked ribose **2** offers, to our view, an attractively short alternate route for the synthesis of formycin analogues.

Experimental Section

General Procedure. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The NMR spectra were obtained on a Varian A-60 or Jeol PS-100 spectrometer with Me_4Si as internal standard. Chemical shifts are reported in parts per million (δ) and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Values given for coupling constants are first order. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Thin layer chromatography (TLC) was performed on microscope slides coated with Merck silica gel GF_{254} and substances were visualized either by uv absorption or by spraying with 20% ethanolic sulfuric acid and charring. Column chromatography was performed by the dry column technique[46] in nylon tubes filled with Woelm silica gel (70–230 mesh) using a 60:1 ratio of absorbent to substance unless otherwise specified.

Silver Acetylides of Methyl and Ethyl Propiolate (4a and 4b). The silver acetylide **4a** (or **4b**) was prepared from the reaction of an ethanolic solution of methyl (or ethyl) propiolate with ammoniacal $AgNO_3$ in the manner described in ref 26a. The precipitated silver acetylide **4a** (or **4b**) was repeatedly washed with H_2O, EtOH, and ether and dried at room temperature[36] over P_2O_5 under vacuum for at least 2 days before use.

Methyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β- and -α-D-ribofuranosyl)propiolate (5a and 6a). To a solution of 13.0 g (0.03

mol) of **2** in 70 ml of anhydrous CH_3CN (dried over molecular sieves 3 Å) were added 9.2 g (0.06 mol) of CCl_4 and 11.8 g (0.045 mol) of $(Ph)_3P$. The mixture was stirred at room temperature until TLC indicated the disappearance of the starting material **2** ($R_f \sim 0.18$ in petroleum ether–EtOAc, 10:1) (usually within 20 min). At this point, 5 g of 3 Å molecular sieves and 13.3 g (0.07 mol) of silver acetylide of methyl propiolate **4a**[26a] were added and the mixture was stirred at room temperature, in the dark, until TLC indicated the disappearance of all the chloro sugar **3** [$R_f \sim 0.45$ for the α anomer and $R_f \sim 0.6$ for the β anomer in petroleum ether (30–60°)–EtOAc,(10:1)]. The reaction took ~10 days. The mixture was then diluted with 200 ml of CH_2Cl_2 and filtered. The filtrate, on evaporation, afforded a thick syrup which partially dissolved on warming with diethyl ether (300 ml) leaving an oil which was removed by filtration through 50 g of silica gel. The filtrate, which contained mainly the β-acetylenic ester **5a** ($R_f \sim 0.36$ in petroleum ether–EtOAc, 10:1) was evaporated to dryness and the residue chromatographed on a dry silica gel column (600 g) using a mixture of petroleum ether–EtOAc (10:1) as eluent.

Compound **5a** was isolated as a syrup (5.14 g, 34%) and was obtained analytically pure by a second chromatography using the same system: λ_{max} (EtOH) 253 nm (ϵ 750), 260 (790), 263 (710) sh, 266 (610) sh, 269 (440) sh; ν_{max} ($CHCl_3$) 2260 (C≡C), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.30 and 1.50, (2 s, 6, CMe_2), 3.28 (m, 2, H-5′), 3.66 (s, 3, COOMe), 4.33 (m, 1, H-4′), 4.62 (dd, 1, H-3′, $J_{2',3'}$ = 5.8, $J_{3',4'}$ = 1.5 Hz), 4.75 (d, 1, H-1′, $J_{1',2'}$ = 2.9 Hz), 4.83 (dd, 1, H-2′), 7.19–7.52 (m, 15, trityl).

Anal. Calcd for $C_{31}H_{30}O_6$ (498.6): C, 74.68; H, 6.07. Found: C, 74.67; H, 6.02.

Elution of a slower moving band afforded 1.15 g (7.6%) of **6a** as a syrup which crystallized on standing. Recrystallization from EtOAc–petroleum ether gave the analytical sample: mp 157–158°; λ_{max} (EtOH) 253 nm (ϵ 570), 259 (670), 262 (560), 266 (480), 269 (310); ν_{max} (KBr) 2265 (C≡C), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.35 and 1.56 (2 s, 6, CMe_2), 3.11 (dd, 1, H-5′ a, $J_{4',5'a}$ = 3.11, $J_{5'a,5'b}$ = 10.2 Hz), 3.43 (dd, 1, H-5′b, $J_{4',5'b}$ = 3.1 Hz), 3.77 (s, 3, COOMe), 4.26 (t, 1, H-4′), 4.70 (d, 1, H-3′, $J_{2',3'}$ = 6.1 Hz), 4.95 (dd, 1, H-2′), 5.18 (d, 1, H-1′, $J_{1',2'}$ = 4.6 Hz), 7.23–7.39 (m, 15, trityl).

Anal. Calcd for $C_{31}H_{30}O_6$ (498.6); C, 74.68; H, 6.07. Found: C, 74.55; H, 6.13.

Ethyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β- and -α-D-ribofuranosyl)propiolate (5b and 6b). Method A. From Compound 2. To a solution of 43.2 g (0.1 mol) of **2** in 250 ml of dried CH_3CN were added 39.4 g (0.15 mol) of $(Ph)_3P$ and 30.8 g (0.2 mol) of CCl_4 and the clear solution was stirred at room temperature until TLC indicated the disappearance of **2** (usually 20 min). A suspension of 43 g (0.21 mol) of the silver derivative of ethyl propiolate **4b**[26a] in dry CH_3CN (160 ml) which had been prestirred with 3 Å molecular sieves (80 g) for 2 hr was then added to the solution of chloro sugar **3** prepared above. This mixture was stirred in the dark until TLC indicated the disappearance of the chloro sugar **3**. This usually takes 5 days. The procedure described above for the isolation of the methyl derivatives **5a** was used to obtain 18.4 g (36%) of **5b** as a syrup. This compound was obtained analytically pure after another chromatography using the same system: λ_{max} (EtOH) 254 nm (ϵ 840), 259 (910), 263 (770), 266 (670), 269 (480); ν_{max} ($CHCl_3$) 2260 (C≡C), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.19 (t, 3, CH_2CH_3), 1.30 and 1.50 (2 s, 6, CMe_2), 3.29 (m, 2, H-5′), 4.13 (q, 2, $COOCH_2$), 4.33 (m, 1, H-4′), 4.62 (dd, 1, H-3′, $J_{2',3'}$ = 5.8, $J_{3',4'}$ = 1.8 Hz), 4.76 (d, 1, H-1′, $J_{1',2'}$ = 2.8 Hz), 4.84 (dd, 1, H-2′), 7.20–7.53 (m, 15, trityl).

Anal. Calcd for $C_{32}H_{32}O_6$ (512.6); C, 74.98; H, 6.29. Found: C, 74.97; H, 6.35.

By the same procedure also was isolated 4.3 g (8.4%) of **6b:** mp 133–134° (from EtOAc–petroleum ether); λ_{max} (EtOH) 253 nm (ϵ 680), 259 (750), 263 (630), 266 (530), 269 (370); ν_{max} (KBr) 2265 (C≡C), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.30 (t, 3, CH_2CH_3), 1.35 and 1.56 (2 s, 6, CMe_2), 3.10 (dd, 1, H-5′a, $J_{4',5'a}$ = 3.1, $J_{5'a,5'b}$ = 10.2 Hz), 3.43 (dd, 1, H-5′b, $J_{4',5'b}$ = 3.0 Hz), 4.24 (m, 3, $COOCH_2$, H-4′), 4.70 (d, 1, H-3′, $J_{2',3'}$ = 6.0 Hz), 4.96 (dd, 1, H-2′), 5.18 (d, 1, H-1′, $J_{1',2'}$ = 4.7 Hz), 7.27–7.38 (m, 15, trityl).

Anal. Calcd for $C_{32}H_{32}O_6$ (512.6): C, 74.98; H, 6.29. Found: C, 75.05; H, 6.31.

Method B. From Compound 3. A suspension of **4b** (4.1 g, 0.2 mol) and of 3 Å molecular sieves (10 g) in a mixture of benzene (40 ml) and CH_2Cl_2 (10 ml) previously dried over molecular sieves was stirred for 20 min at room temperature in the absence of light. The crystalline β anomer of **3**[30] (4.51 g, 0.01 mol) was then added and the reaction mixture was stirred for 40 hr. The products were obtained as described in method A. The isolated compounds **5b** and **6b** weighed 2.27 g (44.5% from **3**) and 0.80 g (15.5%).

5(4)-Carbomethoxy-4(5)-(β-D-ribofuranosyl)-1,2,3-triazole (7). The propiolate derivative **5a** (2.50 g, 5 mmol) was dissolved in 3.0 g (26 mmol) of trimethylsilyl azide and heated in a sealed vessel at 105° for 48 hr. After cooling to room temperature the solution was diluted with 10 ml of MeOH and evaporated to dryness. The residue was triturated with EtOAc and filtered to give **7** (0.823 g, 63%) as a solid which crystallized from CH_3CN: mp 146–147°; λ_{max} (EtOH) 218 nm (ϵ 7660); λ_{max} (pH 13) 235 nm (ϵ 6880); ^1H NMR (Me_2SO-d_6) δ 3.56 (m, 3, H-5′, OH), 3.84 (s, 3, $COOCH_3$), 3.7–4.1 (m, 3, H-2′, H-3′, H-4′), 4.99 (d, 1, OH, $J_{OH,H}$ = 4.9 Hz), 5.15 (d, 1, OH, $J_{OH,H}$ = 5.5 Hz), 5.23 (d, 1, H-1′, $J_{1',2'}$ = 5.2 Hz).

Anal. Calcd for $C_9H_{13}N_3O_6$ (259.2): C, 41.70; H, 5.06; N, 16.21. Found: C, 41.72; H, 5.12; N, 16.22.

5(4)-Carboxamido-4(5)-(β-D-ribofuranosyl)-1,2,3-triazole (8). A solution of 1.30 g (5 mmol) of **7** in 20 ml of MeOH and 20 ml of liquid ammonia was heated at 60° in a sealed vessel for 3 days. The solution was cooled to room temperature and evaporated to dryness to afford, after chromatography (MeOH–EtOAc–$CHCl_3$, 2:1:1) **8** as a syrup (0.98 g, 80%): λ_{max} (EtOH) 210 nm (ϵ 9970); ^1H NMR (Me_2SO-d_6) δ 3.1–4.0 (m, 6, H-2′, H-3′, H-4′, H-5′, OH), 4.91 and 5.12 (2 broad s, 2, OH), 5.27 (d, 1, H-1′, $J_{1',2'}$ = 4.6 Hz), 7.40 and 7.71 (2 s, 2, $CONH_2$).

This compound could not be obtained analytically pure and was further characterized as its tri-*O*-acetyl derivative by treating **8** (0.300 g, 1.2 mmol) in pyridine with acetic anhydride. Subsequent column chromatography (EtOAc–petroleum ether, 3:1) afforded 0.41 g (88%) of 5(4)-carboxamido-4(5)-2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl-1,2,3-triazole. An analytical sample was obtained by a second chromatography using the same solvent system: λ_{max} (EtOH) 209 nm (ϵ 8650); λ_{max} (pH 13) 238 nm (ϵ 7380); ^1H NMR ($CDCl_3$) δ 2.07, 2.09, and 2.09 (3 s, 9, OAc), 4.36 (broad s, 3, H-4′, H-5′), 5.42 (dd, 1, H-3′, $J_{2',3'}$ = 5.0, $J_{3',4'}$ = 5.2 Hz), 5.69 (dd, 1, H-2′), 5.76 (d, 1, H-1′, $J_{1',2'}$ = 4.5 Hz), 6.75 and 7.39 (2 s, 2, $CONH_2$).

Anal. Calcd for $C_{14}H_{18}N_4O_8$ (370.3): C, 45.51; H, 4.90; N, 15.13. Found: C, 45.25; H, 4.90; N, 14.96.

Reaction of Methyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propiolate (5a) with Diazomethane. To 4.0 g (8 mmol) of **5a** in 30 ml of ether at 0°C (ice–water bath) was added 100 ml of a cold, dried ethereal solution of CH_2N_2 (~12–15 mmol). The mixture was kept at 0° for 30 min. It was then treated dropwise with a diluted solution of AcOH in ether until the evolution of nitrogen stopped. Evaporation to dryness and column chromatography of the residue (petroleum ether–EtOAc, 2:1) afforded two products. The major and more polar component was obtained as a white foam (3.15 g, 72%) and identified as 3(5)-carbomethoxy-4-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (**9a**). It crystallized from MeOH with one molecule of crystallization (as shown by NMR), mp 120–125°. Product **9a** also could be obtained in crystalline form (54%) by direct crystallization of the residue from MeOH without chromatography: λ_{max} (pH 13) 232 nm (ϵ 12650), 250 (7830) sh; ^1H NMR ($CDCl_3$) δ 1.34 and 1.60 (2 s, 6, CMe_2), 3.33 (m, 2, H-5′), 3.46 (s, 3, CH_3OH from crystallization), 3.68 (s, 3, $COOCH_3$), 4.26 (m, 1, H-4′), 4.67 (m, 2, H-2′, H-3′), 5.47 (d, 1, H-1′, $J_{1',2'}$ = 2.7 Hz), 7.17–7.54 (m, 15, trityl), 7.83 (s, 1, H-3).

Anal. Calcd for $C_{32}H_{32}N_2O_6 \cdot CH_3OH$ (572.7): C, 69.21; H, 6.34; N, 4.89. Found: C, 69.13; H, 6.31; N, 4.89.

From the column was also isolated 0.14 g of a minor and less polar product (syrup). From the similarity of its NMR spectrum to that of **10b** (vide infra) it was identified as 5-carbomethoxy-4-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-1-methylpyrazole (**10a**) resulting from further reaction of the pyrazole initially formed with CH_2N_2: ^1H NMR ($CDCl_3$) δ 1.31 and 1.59 (2 s, 6, CMe_2), 3.26 (d, 2, H-5′, $J_{4',5'}$ = 4.9 Hz), 3.87 (s, 3, NCH_3), 4.13 (s, 3, $COOCH_3$), 4.22 (m, 1, H-4′), 4.59 (m, 2, H-2′, H-3′), 5.39 (d, 1, H-1′, $J_{1',2'}$ = 3.4 Hz), 7.22–7.57 (m, 16, trityl, H-3).

Reaction of Ethyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propiolate (5b) with Diazomethane. To 0.57 g (1.1 mmol) of **5b** in 5 ml of ether at 0° was added 15 ml of a cold ethereal solution of CH_2N_2 (~1.5 mmol). The mixture was left at 0° for 45 min and treated dropwise with a solution of AcOH in ether. The colorless solution was then evaporated to a syrup which was chromatographed on a dry column of silica gel using petroleum ether–EtOAc (2:1) as eluent. Two products were isolated. Elution of the major component (slower moving) gave 0.451 g (73%) of 3(5)-carbethoxy-4-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (**9b**) as a white foam which crystallized from MeOH with one solvent molecule of crystallization, mp 95–105° (only partial removal of the solvent of crystallization could be achieved by

drying **9b** for 6 days at 80°C): λ_{max} (pH 13) 233 nm (ε 11840), 251 (7850) sh; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3, CH_2CH_3), 1.33 and 1.60 (2 s, 6, CMe_2), 3.33 (m, 2, H-5′), 3.48 (s, 3, CH_3OH crystallization), 4.28 (m, 3, $COOCH_2$, H-4′), 4.65 (m, 2, H-2′, H-3′), 5.84 (d, 1, H-1′, $J_{1',2'}$ = 2.4 Hz), 7.24–7.53 (m, 15, trityl), 7.77 (s, 1, H-3).

Anal. Calcd for $C_{33}H_{34}N_2O_6 \cdot CH_3OH$ (586.7): C, 69.61; H, 6.53; N, 4.77. Found: C, 69.65; H, 6.44; N, 4.78.

Elution of the minor (and less polar) product afforded 0.065 g (10%) of 5-carbethoxy(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-1-methylpyrazole (**10b**) as a syrup. Purification of this compound by a second chromatography (petroleum ether–EtOAc, 6:1) afforded the analytical sample: λ_{max} (EtOH) 248 nm (ε 7129) sh; ^{1}H NMR ($CDCl_3$) δ 1.31 and 1.58 (2 s, 6, CMe_2), 1.40 (t, 3, CH_2CH_3), 3.22 (d, 2, H-5′, $J_{4',5'}$ = 4.6 Hz), 4.16 (s, 3, NCH_3), 4.16 (t, 1, H-4′), 4.38 (q, 2, $COOCH_2$), 4.57 (m, 2, H-2′, H-3′), 5.43 (d, 1, H-1′, $J_{1',2'}$ = 2.8 Hz), 7.23–7.50 (m, 15, trityl), 7.55 (s, 1, H-3).

Anal. Calcd for $C_{34}H_{36}N_2O_6$ (568.7): C, 71.81; H, 6.38; N, 4.93. Found: C, 71.90; H, 6.31; N, 4.87.

3(5)-Carboxamido-4-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (11). A. From 9a. A methanolic solution (5 ml) of **9a** (1.36 g, 2.5 mmol) was added to a mixture of 10 ml of MeOH and 15 ml of liquid ammonia. The mixture was heated in a sealed tube for 3 days at 54°, cooled at room temperature, evaporated to dryness, and dissolved in hot benzene. On cooling 0.808 g (61%) of **11** was obtained as colorless crystals: mp 214–215°; λ_{max} (pH 13) 232 nm (ε 13580), 248 (8990) sh; ^{1}H NMR ($CDCl_3$) 1.36 and 1.59 (2 s, 6, CMe_2), 3.16–3.46 (m, 2, H-5′), 4.27 (m, 1, H-4′), 4.75 (m, 2, H-2′, H-3′), 5.18 (d, 1, H-1′, $J_{1',2'}$ = 4.2 Hz), 5.59 and 7.88 (2 broad s, 2, $CONH_2$) 7.21–7.45 (m, 15, trityl), 7.63 (s, 1, H-3).

Anal. Calcd for $C_{31}H_{31}N_3O_5$ (525.6): C, 70.84; H, 5.94; N, 7.99. Found: C, 70.75; H, 5.85; N, 7.94.

B. From 9b. Similar treatment of **9b** (0.300 g, 0.54 mmol) for 4 days at 72° afforded 0.233 g (82%) of **11** identical in all respects with that obtained by method A.

3(5)-Carboxamido-4-(β-D-ribofuranosyl)pyrazole (12). To a solution of 0.525 g (1 mmol) of **11** in 10 ml in MeOH was added 5 ml of a saturated solution of HCl in MeOH. After standing for 90 min, the reaction mixture was evaporated to dryness and the residue was partitioned between water and $CHCl_3$. The aqueous phase was washed twice with $CHCl_3$ and evaporated to dryness. The residue was redissolved in water and evaporated again, leaving 0.238 g of **12** as a white foam (homogeneous material on TLC). Recrystallization from MeOH afforded a pure sample (0.188 g, 75%) of the known **12**,[29,42] mp 199–201°C (reported 200–202°C,[29] 208–210°C[42]), with physical properties identical with those previously reported for that compound.

3(5)-Carbomethoxy-4-(β-D-ribofuranosyl)pyrazole (13a). A solution of 0.270 g (0.5 mmol) of **9a** in 5 ml of MeOH was treated with 25 ml of a saturated solution of HCl. After standing for 90 min, the product was isolated as described above for the preparation of **12**. The procedure afforded 0.125 g of a crystalline residue. This material was recrystallized from EtOH–ether to give the known **13a**[29] in pure form (0.092 g, 72%), mp 181–182.5°C (reported 186–188°C[29]).

3(5)-Carbethoxy-4-(β-D-ribofuranosyl)pyrazole (13b). Into 13 ml of EtOH containing 0.550 g (1 mmol) of **9b** was dissolved 0.9 g of anhydrous HCl. After 2 hr at room temperature the mixture was processed as described above for the preparation of **12**. Thus 0.270 g of **13b** was obtained as a white foam which crystallized from MeOH–ether to give 0.191 g (70%) of **13b** analytically pure: mp 155–156°; λ_{max} (EtOH) 222 nm (ε 11510), λ_{max} (pH 13) 241 nm (ε10390); ^{1}H NMR (Me_2SO-d_6) δ 1.30 (t, 3, CH_2CH_3), 3.32–3.86 (m, 5, H-2′, H-3′, H-4′, H-5′), 4.27 (q, 2, $COOCH_2$), 4.75 (broad s, 3, OH's), 5.09 (d, 1, H-1′, $J_{1',2'}$ = 3.7 Hz), 7.90 (s, 1, H-3).

Anal. Calcd for $C_{11}H_{16}N_2O_6$ (272.3): C, 48.53; H, 5.92; N, 10.29. Found: C, 48.59; H, 6.07; N, 10.16.

5-Carbethoxy-1-methyl-4-(β-D-ribofuranosyl)pyrazole (14b). To 50 ml of an ethanolic solution of **10b** (0.57 g, 1 mmol) was added 5 ml of a saturated solution of HCl in EtOH. After 2 hr at room temperature the mixture was treated as described previously to afford 0.19 g (66%) of a syrup which crystallized from MeOH–ether to give analytically pure **14b**: mp 144–146°; λ_{max} (EtOH) 233 nm (ε 8680), 246 (ε 6800) sh; λ_{max} (pH 13) 236 nm (ε5130); ^{1}H NMR (Me_2SO-d_6) δ 1.33 (t, 3, CH_2CH_3), 3.56 (m, 2, H-5′), 3.72–4.41 (m, 8, H-2′, H-3′, H-4′, 3 OH's, $COOCH_2$), 4.03 (s, 3, NCH_3), 5.06 (d, 1, H-1′, $J_{1',2'}$ = 4.6 Hz), 7.67 (s, 1, H-3).

Anal. Calcd for $C_{12}H_{18}N_2O_6$ (286.3): C, 50.35; H, 6.34; N, 9.79. Found: C, 50.28; H, 6.32; N, 9.80.

Reaction of Methyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propiolate (5a) with Ethyl Diazoacetate (15). A mixture of 1.05 g (2.1 mmol) of **5a** and 0.93 g (8 mmol) of **15** was heated at 50° for 20 hr. The mixture was then cooled at room temperature for 2 hr and the crystalline product which had precipitated was filtered and washed twice with ether (2 × 2 ml) to give 0.606 g (46%) of 3(5)-carbethoxy-5(3)-carbomethoxy-4-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (**16**). Recrystallization from EtOAc–petroleum ether afforded the analytical sample: mp 202–204°; λ_{max} (pH 13) 254 nm (ε 9660); ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.61 (2 s, 6, CMe_2), 1.34 (t, 3, CH_2CH_3), 3.20 (dd, 1, H-5′a, $J_{4',5'a}$ = 4.1 Hz, $J_{5'a,5'b}$ = 9.7 Hz), 3.42 (dd, 1, H-5′b, $J_{4',5'b}$ = 7.3 Hz), 3.74 (s, 3, $COOCH_3$), 4.01–4.38 (m, 3, H-4′, $COOCH_2$), 4.25 (dd, 1, H-3′, $J_{2',3'}$ = 7.3, $J_{3',4'}$ = 5.5 Hz), 4.75 (dd, 1, H-2′), 5.81 (d, 1, H-1′, $J_{1',2'}$ = 5.0 Hz), 7.19–7.52 (m, 15, trityl).

Anal. Calcd for $C_{35}H_{36}N_2O_8$ (612.7): C, 68.61; H, 5.92; N, 4.57. Found: C, 68.66; H, 5.91; N, 4.52.

The filtrate and washings were combined and chromatographed on dry column (petroleum ether–EtOAc, 2:1) to afford 0.186 g of a slower moving product identical with **16** (total yield 61%) and 0.195 g (15%) of a faster moving product which after crystallization from EtOAc–petroleum ether (mp 183–184°) was identified as 3(5)-carbethoxy-4-carbomethoxy-5(3)-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (**17**): λ_{max} (pH 13) 230 nm (ε 11460) sh, 253 (9200); ^{1}H NMR ($CDCl_3$) δ 1.34 and 1.60 (2 s, 6, CMe_2), 1.39 (t, 3, CH_2CH_3), 3.06 (dd, 1, H-5′a, $J_{4',5'a}$ = 6.6, $J_{5'a,5'b}$ = 10.8 Hz), 3.44 (dd, 1, H-5′b, $J_{4',5'b}$ = 3.5 Hz), 3.83 (s, 3, $COOCH_3$), 4.41 (m, 3, H-4′, $COOCH_2$), 4.59 (dd, 1, H-3′, $J_{2',3'}$ = 5.5, $J_{3',4'}$ = 3.3 Hz), 4.83 (dd, 1, H-2′), 5.52 (d, 1, H-1′, $J_{1',2'}$ = 2.8 Hz), 7.25–7.50 (m, 15, trityl).

Anal. Calcd for $C_{35}H_{36}N_2O_8$ (612.7): C, 68.61; H, 5.92; N, 4.57. Found: C, 68.82; H, 5.81; N, 4.71.

When this reaction was carried out at room temperature for 3 days, the same procedure of isolation and purification afforded **16** and **17** in 63 and 10.3% yield, respectively.

Reaction of Ethyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propiolate (5b) with Methyl Diazoacetate (18). A mixture of 0.700 g (1.37 mmol) of **5b** and 0.460 g (4.6 mmol) of **18** was heated at 50° for 2 days. The mixture was then cooled at room temperature for 2 hr and the crystalline product which had precipitated was filtered and washed twice with ether (2 × 2 ml) to give 0.369 g (44%) of **16**. The filtrate and washings were combined and chromatographed on a dry column (petroleum ether–EtOAc, 2:1) to give 0.086 g of **16** (total yield 54.4%) and 0.112 g (13.3%) of a faster moving product which after crystallization from EtOAc–petroleum ether (mp 159–161°) was identified as 4-carbethoxy-3(5)-carbomethoxy-5(3)-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (**19**): λ_{max} (pH 13) 230 nm (ε 11890) sh, 252 (9800); ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.59 (2 s, 6, CMe_2), 1.33 (t, 3, CH_2CH_3), 3.07 (dd, 1, H-5′a, $J_{4',5'a}$ = 6.8, $J_{5'a,5'b}$ = 10.8 Hz), 3.47 (dd, 1, H-5′b, $J_{4'5'b}$ = 3.4 Hz), 3.93 (s, 3, $COOCH_3$), 4.32 (q, 2, $COOCH_2$), 4.42 (m, 1, H-4′), 4.60 (dd, 1, H-3′, $J_{2',3'}$ = 6.1, $J_{3',4'}$ = 3.7 Hz), 4.84 (dd, 1, H-2′), 5.55 (d, 1, H-1′, $J_{1',2'}$ = 2.4 Hz), 7.26–7.51 (m, 15, trityl).

Anal. Calcd for $C_{35}H_{36}N_2O_8$ (612.7): C, 68.61; H, 5.92; N, 4.57. Found: C, 68.68; H, 5.89; N, 4.53.

When this reaction was carried out at room temperature for 9 days and the same subsequent procedure was followed, **16** and **19** were obtained in 56 and 8.3% yield, respectively.

Registry No. —**2**, 55726-19-7; **4a**, 57031-37-5; **4b**, 57016-89-4; **5a**, 57016-90-7; **5b**, 57016-91-8; **6a**, 57016-92-9; **6b**, 57016-93-0; **7**, 57049-19-1; **8**, 57016-94-1; 8 triacetate, 57016-95-2; **9a**, 57016-96-3; **9b**, 57016-97-4; **10a**, 57016-98-5; **10b**, 57016-99-6; **11**, 57017-00-2; **12**, 50720-82-6; **13a**, 50866-58-5; **13b**, 57017-01-3; **14b**, 57017-02-4; **15**, 623-73-4; **16**, 57017-03-5; **17**, 57017-04-6; **18**, 6832-16-2; **19**, 57017-05-7; trimethylsilyl azide, 4648-54-8; diazomethane, 334-88-3.

References and Notes

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U.S. Public Health Service (Grant CA 08748 and 17085); Fellowship from Program of Cultural Cooperation between U.S.A. and Spain (F. G. D. L. H), and Fellowship Montgomery Fund (S.Y-K.T.).

(2) R. J. Suhadolnik "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970.

(3) (a) T. Haneishi, T. Okazaki, T. Hata, C. Tamura, M. Nomura, A. Naito, I. Seki, and M. Arai, *J. Antibiot.*, **24**, 797 (1971); (b) Y. Kusakabe, J. Nagatsu, M. Shibuya, O. Kawaguchi, C. Hirose, and S. Shirato, *ibid.*, **25**, 44 (1972); (c) K. Sasaki, Y. Kusakabe, and S. Esumi, *ibid.*, **25**, 151 (1972).

(4) R. W. Chambers, *Prog. Nucleic Acid Res. Mol. Biol.*, **5**, 349 (1966).

(5) M. Bobek, J. Farkas and F. Sorm, *Collect. Czech. Chem. Commun.*, **34**, 1690 (1969).

(6) R. A. Long, A. F. Lewis, R. K. Robins, and L. B. Townsend, *J. Chem. Soc. C*, 2443 (1971).
(7) U. Lerch, M. G. Burdon, and J. G. Moffatt, *J. Org. Chem.*, **36**, 1507 (1971).
(8) W. A. Asbun and S. B. Binkley, *J. Org. Chem.*, **33**, 140 (1968).
(9) S. David and A. Lubineau, *C. R. Acad. Sci., Ser. C*, **275**, 331 (1972).
(10) M. P. Mertes, J. Zielinski, and C. Pillar, *J. Med. Chem.*, **10**, 320 (1967).
(11) (a) L. Kalvoda, J. Farkas, and F. Sorm, *Tetrahedron Lett.*, 2297 (1970); (b) G. Trummlitz and J. G. Moffatt, *J. Org. Chem.*, **38**, 1841 (1973).
(12) E. M. Acton, K. J. Ryan, D. W. Henry, and L. Goodman, *Chem. Commun.*, 986 (1971).
(13) J. Farkas and F. Sorm, *Collect. Czech. Chem. Commun.*, **37**, 2798 (1972).
(14) J. Farkas, Z. Flegelová, and F. Sorm, *Tetrahedron Lett.*, 2279 (1972).
(15) (a) J. G. Buchanan, A. R. Edgar, and M. J. Power, *J. Chem. Soc., Perkin Trans. 1*, 1943 (1974), and references cited therein; (b) J. G. Buchanan, A. R. Edgar, M. J. Power, and P. D. Theaker, *Carbohydr. Res.*, **38**, C22 (1974).
(16) R. Zelinski and R. E. Meyer, *J. Org. Chem.*, **23**, 810 (1958).
(17) D. Horton, J. B. Hughes, and J. K. Thomson, *J. Org. Chem.*, **33**, 728 (1968), and references cited therein.
(18) H. El Khadem, D. Horton, and M. H. Meshreki, *Carbohydr. Res.*, **16**, 409 (1971).
(19) J. M. Tronchet, A. Gonzalez, J. B. Zumwald, and F. Perret, *Helv. Chim. Acta*, **57**, 1505 (1974).
(20) M. T. Garcia-Lopez, G. Garcia-Muñoz, and R. Madroñero, *J. Heterocycl. Chem.*, **8**, 525 (1971).
(21) For a general review on 1,3-dipolar cycloaddition see (a) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565, 633 (1963). (b) For a more recent review on 1,3-dipolar cycloaddition to alkynes see J. Bastide, J. Hamelin, F. Texier, and Y. V. Quang, *Bull. Soc. Chim. Fr.*, 2555, 2871 (1973).
(22) S. Y-K. Tam, F. G. De Las Heras, R. S. Klein, and J. J. Fox, *Tetrahedron Lett.*, 3271 (1975).
(23) (a) A. N. Kost and I. I. Grandberg, *Adv. Heterocycl. Chem.*, **6**, 347 (1966); (b) R. Fusco, "The Chemistry of Heterocyclic Compounds", Vol. 22, A. Weissberger, Ed., Interscience, New York, N.Y., 1967.
(24) (a) R. P. Barnes, "Heterocyclic Compounds", Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1952, Chapter 7; (b) N. K. Kochetkov and S. D. Sokolov, *Adv. Heterocycl. Chem.*, **2**, 365 (1963).
(25) Of notable exception are two novel methods involving (a) a one-step reaction between an aldehydo sugar and dimethyl diazomethyl phosphonate and (b) treatment of the same sugar with $(Ph)_3P{=}CBr_2$ and then with *n*-BuLi. See ref 19.
(26) (a) CIBA Ltd., Belgian Patent 620,022; *Chem. Abstr.*, **59**, 8840*f* (1963). (b) For a general procedure on the preparation of silver acetylides and their reaction with acyl halides see R. B. Davis and D. H. Scheiber, *J Am. Chem. Soc.*, **78**, 1675 (1956).
(27) R. S. Klein, M. P. Kotick, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **36**, 4113 (1971).
(28) S. Hanessian and A. G. Pernet, *Can. J. Chem.*, **52**, 1266 (1974).
(29) H. P. Albrecht, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.*, **39**, 2176 (1974).
(30) (a) H. Ohrui and J. J. Fox, *Tetrahedron Lett.*, 1951 (1973); (b) R. S. Klein, H. Ohrui, and J. J. Fox, *J. Carbohydr., Nucleosides, Nucleotides*, **1**, 265 (1974).
(31) (a) Although the terms anomeric and anomer do not strictly apply to *C*-glycosyl derivatives, they are nevertheless used here for the sake of simplicity and convenience. (b) The chosen nomenclature for **5b** and **6b**, in our opinion, is more readily understandable than the alternative: ethyl 4,7-anhydro-5,6-*O*-isopropylidene-8-*O*-trityl-D-*allo*- and -*altro*-oct-2-ynoate.
(32) Note Added in Proof. After submission of the present manuscript, a preliminary communication on the synthesis of methyl 3-(2,3,5-tri-*O*-benzyl-α- and -β-D-ribofuranosyl)propiolate by J. G. Buchanan, A. R. Edgar, M. J. Power, and G. C. Williams appeared: *J. Chem. Soc., Chem. Commun.*, 501 (1975).
(33) L. B. Townsend in "Synthetic Procedures in Nucleic Acid Chemistry", Vol. 2, W. W. Zorbach and R. S. Tipson, Ed., Wiley-Interscience, New York, N.Y., 1973, p 330.
(34) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, *J. Am. Chem. Soc.*, **97**, 4602 (1975). The authors are indebted to Dr. Moffatt of the Institute of Molecular Biology, Syntex Research, Palo Alto, Calif., for access to the manuscript prior to publication.
(35) J. L. Imbach and B. L. Kam, *J. Carbohydr., Nucleosides, Nucleotides*, **1**, 271 (1974).
(36) The first attempt to dry the silver acetylide of ethyl propiolate at higher temperatures (70°, in vacuo) resulted in its spontaneous decomposition and the formation of large amounts of metallic silver. Although no detonation was heard and no glassware was damaged, we recommend that such acetylides be handled with caution and dried only as described in the text.
(37) (a) R. G. Weis and E. T. Snyder, *J. Org. Chem.*, **35**, 1627 (1970); (b) R. Appel, R. Kleinstuck, K. Ziehn, and F. Knoll, *Chem. Ber.*, **103**, 3631 (1970).
(38) **2** (0.227 mmol), 0.274 mmol of $(Ph)_3P$, and 0.45 mmol of CCl_4 were dissolved in 0.5 ml of $CDCl_3$ and the reaction was followed by NMR with a Varian A-60 spectrometer (1% Me_4Si as internal standard).
(39) T. L. Gilchrist and G. E. Gymer, *Adv. Heterocycl. Chem.*, **16**, 33 (1974).
(40) (a) L. Birkofer and A. Ritter, *Angew. Chem. Int. Ed. Engl.*, **4**, 417 (1965); (b) L. Birkofer and P. Wegner, *Chem. Ber.*, **99**, 2512 (1966).
(41) See ref 23a, p 414–416, and references cited therein.
(42) G. Just and M. Ramjeesingh, *Tetrahedron Lett.*, 985 (1975).
(43) (a) R. A. Firestone, *J. Org. Chem.*, **33**, 2285 (1968); (b) R. Huisgen, *Ibid.*, **33**, 2291 (1968); (c) J. Bastide, N. El Ghandour, and O. Henri-Rousseau, *Bull. Soc. Chim. Fr.*, 2290 (1973); (d) J. Bastide and O. Henri-Rousseau, *Ibid.*, 2294 (1973).
(44) K. von Auwers and O. Ungemach, *Ber.*, **66B**, 1205 (1933).
(45) J. Bastide, N. El Ghandour, and O. Henri-Rousseau, *Tetrahedron Lett.*, 4225 (1972).
(46) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).

Nitrite Esters of Polyhydroxy Polymers[1]

Richard G. Schweiger

Stauffer Chemical Company, Oxnard, California 93030

Received June 16, 1975

Nitrite esters of polysaccharides and synthetic polyhydroxy polymers are obtained by reaction of polyhydroxy polymer with dinitrogen tetroxide or nitrosyl chloride in a medium containing a suitable proton acceptor. The polymeric nitrite esters are relatively unstable compounds and can be isolated only at low temperatures as wet, fibrous materials from a neutral or alkaline medium. In the presence of a protic solvent, such as water or alcohol, and catalytic amounts of mineral acid, they decompose immediately with formation of nitrous acid or alkyl nitrite and regeneration of the corresponding polyhydroxy polymer. Results suggest that nitrosation of alcoholic hydroxyl groups, irrespective of their origin, follows the same mechanism and is subject to an equilibrium $ROH + N_2O_4 \rightleftharpoons RONO + HNO_3$, whose equilibrium constant depends greatly on the stability of the nitrite ester.

It has been found previously that cellulose can be solubilized with nitrogen dioxide or nitrosyl chloride in *N,N*-dialkylacylamide, with formation of clear and viscous solutions.[2] More recent results indicate that the reason for this solvation lies in the formation of cellulose trinitrite ester, a compound that decomposes immediately in the presence of a protic solvent and mineral acid as a catalyst with regeneration of the cellulose.[3] A reaction mechanism has been proposed[3] in which the nitrosyl nitrate form,[4] not the symmetric nitrogen dioxide dimer, is the reactive agent that quantitatively esterifies the cellulose molecule. Nitrosyl chloride reacts in a similar fashion producing nitrite ester and, instead of nitrate ion, chloride ion. However, a 2.5- to 3-fold excess of nitrosyl chloride is required for completion of the reaction probably as a result of a higher stability, i.e., lower reactivity, of nitrosyl chloride.

It is postulated that the *N,N*-dialkylacylamide functions as a proton acceptor, so the equilibrium as shown in Scheme I would shift to the right to provide for an essentially quantitative nitrite ester formation. Consistent with this mechanism, the rate of esterification increases and the conversion with nitrosyl chloride can be completed with