C-Glycosyl Nucleosides. IV.[1] Syntheses of Several 4-(β-D-Ribofuranosyl)pyrazoles

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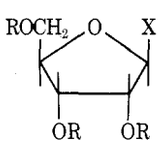
Condensation of several derivatives of 2,5-anhydro-D-allose with phosphoranes gives, *e.g.*, methyl *trans*-4,7-anhydro-5,6,8-tri-*O*-benzoyl-2,3-dideoxy-D-*allo*-oct-2-enonate (4) in high yield. 1,3-Dipolar cycloaddition of 4 with diazomethane followed by dehydrogenation with chlorine readily gives 3(5)-carbomethoxy-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazole (6). The latter can be deblocked to give several different pyrazole *C*-glycosyl nucleosides. Similar cycloaddition of 4 with alkyl diazoacetates leads to some comparable 3,5-disubstituted 4-ribofuranosylpyrazoles. By using the 2-bromo derivative of 4, pyrazoles such as 6 are directly formed by spontaneous dehydrobromination of the intermediate pyrazoline. Condensation of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide with the silver derivatives of alkyl propiolates leads primarily to 1,2-*O*-(α-alkynylbenzylidene) derivatives rather than to ribosylalkynes.

The presence of significant amounts of pseudouridine in transfer RNA[2] and the isolation of a number of nucleoside antibiotics[3] such as formycin, showdomycin, pyrazomycin, and oxazinomycin has stimulated much interest in the synthesis of *C*-glycosyl nucleosides. Syntheses of pseudouridine[4] and of its sugar[5] and base[6] analogs have been achieved *via* direct condensation of suitable derivatives of the heterocyclic base and the pentose moiety. In addition, valuable progress has been made in the direct, Lewis acid catalyzed ribosidation of aromatic and certain heteroaromatic systems.[7]

A perhaps more versatile route for the synthesis of *C*-glycosyl nucleosides involves the elaboration of the desired heterocyclic systems starting from suitably functionalized anhydro sugars (1). Since the carbon–carbon bond ultimately joining the sugar and heterocycle is already present in the starting sugar, this route permits the formation of anomerically pure *C*-glycosides. Using this general method, syntheses of showdomycin[8] and pyrazomycin[9] have been achieved *via* the keto ester **1a**, while the diazo sugar **1b** has been converted into formycin B[10] and oxoformycin.[11]

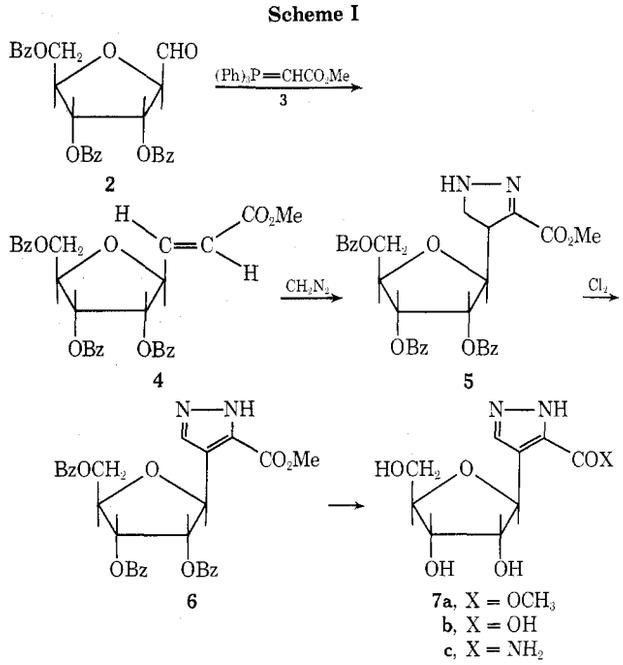


1a, R = Ac; X = $COCO_2Me$
b, R = $CH_2C_6H_5$; X = CHN_2
c, R = $CH_2C_6H_5$; X = CHO
d, R = $CH_2C_6H_5$; X = $COCO_2Me$

In a recent paper[12] we have described the facile synthesis of a variety of derivatives of 2,5-anhydro-D-allose (**1**, X = CHO) in which the hydroxyl functions are protected as esters, acetals, or benzyl ethers. In a subsequent publication, Montgomery, *et al.*,[13] have also described a similar route to derivatives of 2,5-anhydro-D-allose. Under the conditions that were used, however, these workers observed extensive epimerization of the formyl group. We have shown that the tri-*O*-benzyl ether (**1c**) can be readily converted to the keto ester **1d** and thence to showdomycin *via* a Wittig reaction.[1] In this paper we describe the conversion of several derivatives of 2,5-anhydro-D-allose into substituted 4-β-D-ribofuranosylpyrazoles. Previously pyrazoles substituted at C_3 by anhydroalditols have been described *via* reactions of acetylenes with either diazo-[10,14] or nitrilimino[15] sugars. A few acyclic pyrazole-3-polyols have also been prepared by similar routes.[16] The only previous example of a 4-glycosylpyrazole appears to have resulted from the reaction of diazomethane with 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-phenylacetylene by García-Lopez, *et al.*[17]

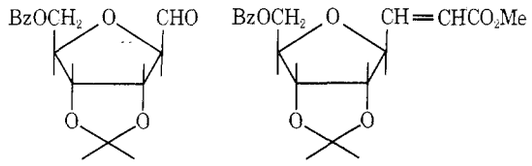
Of the various methods available for the synthesis of 4-substituted pyrazoles[18] the 1,3-dipolar cycloaddition of diazoalkanes to suitably activated β-D-ribofuranosylolefins or -acetylenes appeared to be most applicable for our purposes. The sequence used is outlined in Scheme I. Methyl *trans*-4,7-anhydro-5,6,8-tri-*O*-benzoyl-2,3-dideoxy-D-*allo*-oct-2-enonate (4) appeared to be a suitable dipolarophile[19] for the above type of reaction. This compound was readily prepared by condensation of freshly prepared 3,4,6-tri-*O*-benzoyl-2,5-anhydro-D-allose (**2**)[12] with carbomethoxymethylenetriphenylphosphorane (**3**)[20] in methylene chloride. Following chromatography on silicic acid, 4 was obtained in 91% yield as a homogeneous syrup. Examination by nmr spectroscopy showed that 4 was the pure trans isomer, C_2 H and C_3 H appearing as sharp doublets of doublets at 6.24 and 7.06 ppm with $J_{2,3}$ = 15.5 Hz.[21]

Scheme I

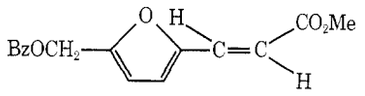


The condensation of the phosphorane **3** with 2,5-anhydro-6-benzoyl-3,4-*O*-isopropylidene-D-allose (**8**),[12] however, gave the unsaturated ester **9** as an 8:1 mixture of its trans and cis isomers in a combined yield of 88%. An

analysis of the isomeric mixture was readily apparent from its nmr spectrum and was most easily revealed by the methyl ester singlets which appeared at 3.73 and 3.80 ppm for the trans and cis isomers, respectively. An attempted alternative synthesis of 4 *via* base-catalyzed condensation of the tribenzoate 2 with trimethyl phosphonoacetate was accompanied by extensive loss of benzoyl groups. Following rebenzoylation, the only pure compound isolated proved to be 2-benzoyloxymethyl-5-(*trans*-carbomethoxyethylene)furan (10). The crystalline product so obtained was shown by its nmr spectrum to be the pure trans isomer with $J_{2,3}$ = 16 Hz.[21] Clearly either the aldehydo group of 2 or the unsaturated ester function in the primary product (4) provided sufficient activation to promote base-catalyzed elimination of benzoyl groups leading to the furan. As expected, the elimination reaction was avoided in the corresponding reaction of trimethyl phosphonoacetate with the isopropylidene derivative 8. From this reaction a 3:1 mixture of the trans and cis isomers of 9 was obtained in 45% yield. From the above it is clear that from the point of view of both yield and isomeric purity, use of the phosphorane 3 constitutes the method of choice for preparation of the unsaturated esters 4 and 9.



8 9



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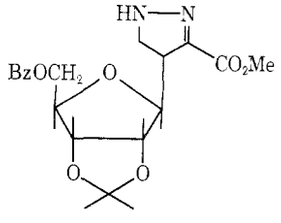
The unsaturated ester 4 underwent a facile 1,3-dipolar cycloaddition with an excess of diazomethane at 0°. Evaporation of the solvent left the crude 2-pyrazoline 5 in essentially quantitative yield. While 5 could be freed of minor impurities by chromatography on silicic acid, its nmr spectrum clearly showed it to be the expected mixture of tautomers which was reflected in multiple signals for several protons. Accordingly the direct dehydrogenation of 5 to the pyrazole 6 was investigated under a variety of conditions.[18] The most effective method by far proved to be the reaction of a dilute solution of the 2-pyrazoline with 2–10 molar equiv of freshly prepared chlorine in carbon tetrachloride. Under these conditions, 5 was converted to crystalline 3(5)-carbomethoxy-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazole (6) in an overall yield of 86% from the unsaturated ester 4. In our experience, the use of bromine, which is commonly employed for such dehydrogenations,[22] rather than chlorine leads to capricious results. We have also investigated the dehydrogenation of the crude 2-pyrazoline 11 resulting from the reaction of 9



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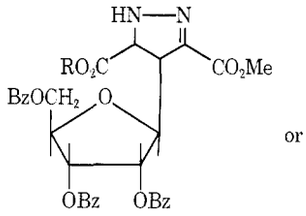
with diazomethane. In this case the use of chlorine or bromine, either alone or buffered by addition of sodium bicarbonate or tertiary amines, led to the formation of by-products. Other attempts using mercuric oxide, lead oxide, chloranil, and DDQ led to incomplete dehydrogenation or competing reactions. While alternative syntheses of the desired isopropylidene pyrazole 19 will be described later in this paper, we have found the tribenzoyl derivative 5 to be a suitable substrate for subsequent reactions.

Treatment of 6 with methanolic sodium methoxide led to facile methanolysis of the benzoate esters and isolation of crystalline 3(5)-carbomethoxy-4-(β-D-ribofuranosyl)pyrazole (7a) in 87% yield. Hydrolysis of 7a, or of the tribenzoate 6, with aqueous sodium hydroxide gave the free pyrazolecarboxylic acid 7b, which was not obtained in crystalline form either as the free acid or as its cyclohexylammonium salt. While 7b as directly obtained was apparently quite pure as judged by its chromatographic and electrophoretic homogeneity, it did not give an elemental analysis within acceptable limits (N roughly 2% low). Its nmr spectrum showed very sharp signals for both C_1· H and the pyrazole ring proton and it would appear that there is an inorganic impurity present. All attempts to effect purification by preparative tlc were unsuccessful, since elution of this very polar substance led to contamination by silicic acid. While isolation of analytically pure 7b was not achieved, its structure was confirmed by re-formation of the crystalline methyl ester 7a upon treatment with methanolic hydrogen chloride.

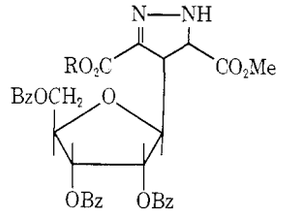
In view of the known biological activities of several nucleosides bearing carboxamido substituents on the heterocyclic ring,[23] it was of interest to prepare the amide 7c. This crystalline compound could be prepared in 70% yield by treatment of the fully blocked methyl ester 6 with saturated methanolic ammonia at room temperature. Interestingly enough, this reaction required 5 days at room temperature to reach completion and examination of aliquots after shorter periods suggested that conversion of the methyl ester to the amide was the slowest step. Thus 7a was the principal product detected after a 2-day treatment. The amide 7c was also obtained by treating the triol methyl ester 7a with liquid ammonia at 100°.

The unsaturated ester 4 also underwent cycloaddition with ethyl diazoacetate, although, as expected,[19] the reaction was much slower than that with diazomethane. By chromatography on silicic acid a tlc-homogeneous mixture of pyrazoline isomers or tautomers (12a or 12′a) was isolated in 64% yield. In the nmr spectrum of 12a or 12′a the

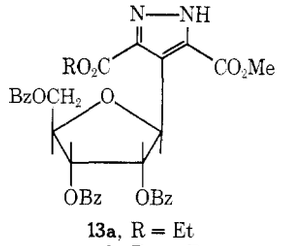


12a, R = Et
b, R = *t*-Bu

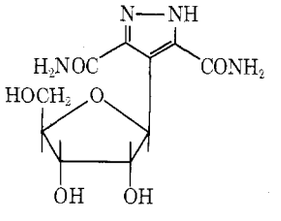
or



12′a, R = Et
b, R = *t*-Bu



13a, R = Et
b, R = *t*-Bu



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sugar protons were largely superimposed upon each other and the only signal that could be used to demonstrate the

mixture of isomers was that from the CH_2 group of the ethyl ester, which appeared as two clearly resolved quartets at 4.08 and 4.19 ppm. The mixture could be obtained in crystalline form but without any apparent change in the isomeric composition. Dehydrogenation was readily effected with chlorine to give 3(5)-carboethoxy-5(3)-carbomethoxy-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazole (**13a**) in 75% yield. In this case the dehydrogenation could also be done quite satisfactorily (65% yield) using bromine. Treatment of **13a** with methanolic ammonia at 100° gave the extremely insoluble crystalline diamide **14** in 44% yield.

The mechanism and direction of addition of diazoalkanes to activated olefins has been extensively studied.[19,24,25] Most commonly the addition appears to be electronically controlled, leading to pyrazoles with nitro-

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EXPERIMENTAL

General Methods

The general methods used are essentially as described in previous papers in this series[1]. We are particularly grateful to Dr. M. L. Maddox and Mrs. J. Nelson for their continuous cooperation concerning nmr spectroscopy.

Methyl *trans*-4,7-anhydro-5,6,8-tri-*O*-benzoyl-2,3-dideoxy-D-*allo*-oct-2-enonate (4)

A solution of p-toluenesulfonic acid monohydrate (14.6 g, 76.6 mmol) in acetone (50 ml) was added at 0° to a solution of 1,3-diphenyl-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazolidine (17.0 g, 25.5 mmol)[12] in methylene chloride (500 ml). After 45 min at room temperature the mixture was filtered and the precipitate was washed with methylene chloride. Solid sodium bicarbonate (2 g) was added to the combined filtrates which were then refiltered and evaporated to dryness leaving 5[12] as a syrup that was essentially homogeneous by tlc using ether-hexane (2:1). This material was dissolved in methylene chloride (150 ml) and to it was added a solution of carbomethoxymethylenetriphenylphosphorane (17.0 g, 51 mmol)[20] in methylene chloride (150 ml). After 2 hr at room temperature the solvent was evaporated and the residue was partitioned between chloroform and water. The organic phase was evaporated to dryness and the residue was dissolved in methylene chloride–ether (1:1, 100 ml) and filtered to remove excess 3. The filtrate was evaporated and the residue was chromatographed on a column of silicic acid using ether-hexane (1:1). The resulting product was evaporated leaving 12.3 g (91%) of 4 as a chromatographically homogeneous clear syrup: $[\alpha]_D^{23}$ −38.6°

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Anal. Calcd. for $C_{18}H_{14}O_5$ (286.27): C, 67.12; H, 4.93
Found: C, 66.98; H, 4.83

3(5)-Carbomethoxy-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-pyrazole (6)

(a) A solution of 4 (5.3 g, 10 mmol) in 25 ml of ether was cooled to 0° and to it was added a solution of diazomethane (~1.0 g by titration, 23 mmol) in ether (80 ml). The resulting solution was stored at 0° for 2 hr and then evaporated to dryness leaving 5.8 g (quant.) of the 2-pyrazoline (5) as an essentially homogeneous (tlc, ether-hexane, 2:1) white foam, the nmr spectrum of which indicated the presence of several tautomers. This material was directly dissolved in dry carbon tetrachloride (100 ml) and to it was added dropwise, with stirring, a freshly prepared, anhydrous solution of chlorine (1.6 g, 23 mmol) in carbon tetrachloride (300 ml). After the addition was complete (1 hr) a small amount of syrup that had separated was dissolved in chloroform (5 ml) and re-added to the reaction mixture. After 1.5 hr at room temperature the solvent was evaporated and the resulting foam was crystallized from chloroform-hexane giving 4.9 g (86%) of 6 with mp 80–81° unchanged upon recrystallization: λ_{max}^{MeOH} 229 nm (ε 45,800), 274 nm (ε 2,900), 281 nm (ε 2,400); $[\alpha]_D^{23}$ 41.7° (c 0.2, $CHCl_3$); nmr ($CDCl_3$) 3.73 ppm (s, 3, OMe), 4.70 (~, 3, $C_{4'}H$, $C_{5'}H_2$), 5.80 (s, 3, $C_{1'}H$, C_2H, C_3H), 7.4 (m, 9, Ar), 7.87 (s, 1, $C_{5(3)}H$), 8.0 (m, 6, Ar).

Anal. Calcd. for $C_{31}H_{26}N_2O_9$ (570.53): C, 65.26; H, 4.59; N, 4.91
Found: C, 65.36; H, 4.61; N, 4.67

(b) A solution of bromine (2.26 g, 14 mmol) in ether (20 ml) was added dropwise to a solution of crude 5 (5.2 g from 9.4 mmol of 4) in ether (100 ml) in the presence of solid sodium bicarbonate (2.5 g). After 10 min at room

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temperature water was added and the mixture was partitioned between chloroform and water. Evaporation of the chloroform layer left a yellow syrup which gave three spots upon tlc (chloroform-ethyl acetate, 10:3). The least polar component was isolated by chromatography on silicic acid using the above solvent giving 2.8 g of a tlc homogeneous product that was crystallized from chloroform-hexane giving 2.1 g (39%) of 6 with mp 80–81° and identical to that from (a) above.

3-Carbomethoxy-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyrazoline (5)

A sample of the crude pyrazoline from the reaction of 4 and diazomethane as above was converted to an analytical sample by preparative tlc using chloroform–methanol (97:3). Elution of the ultraviolet absorbing band with acetone followed by evaporation of the solvent, filtration of a solution of the residue in chloroform and re-evaporation left 5 as a white froth: λ_{max}^{MeOH} 225 nm (ε 35,300), 275 nm (ε 5,900), 282 nm (ε 5,300), 296 nm (ε 5,300); $[\alpha]_D^{23}$ −31.5° (c 0.6, $CHCl_3$); nmr ($CDCl_3$) suggested a mixture of isomers as indicated by multiple signals, e.g., methyl ester singlets at 3.66 and 3.67 ppm.

Anal. Calcd. for $C_{31}H_{28}N_2O_9$ (572.56): C, 65.03; H, 4.93
Found: C, 64.88; H, 5.04

3(5)-Carbomethoxy-4-(β-D-ribofuranosyl)-pyrazole (7a)

A solution of 6 (1.14 g, 2 mmol) in methanol (100 ml) containing sodium methoxide (5 ml of 0.5 M, 2.5 mmol) was stored at room temperature for 24 hr. It was then neutralized by stirring with dried Dowex 50 (H^+) resin, filtered and evaporated. The residue was partitioned between water (100 ml) and chloroform (40 ml) and the aqueous phase was extracted twice with chloroform (20 ml). Evaporation of the aqueous phase left a crystalline residue that was recrystallized from ethanol giving 450 mg (87%) of 7a with mp 186–188°.

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elemental analyses within acceptable limits. Attempted purification by preparative tlc led to some contamination with silica gel.

3(5)-Carboethoxy-5(3)-carbomethoxy-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyrazoline (12a, 12'a)

A solution of 4 (5.3 g, 10 mmol) and ethyl diazoacetate (3.0 g, 26.5 mmol) in ether (100 ml) was heated under reflux for 72 hr. The solvent was then evaporated and the residue was chromatographed on a column of silicic acid using ether–hexane (3:1) giving 4.1 g (64%) of a chromatographically homogeneous mixture of pyrazoline tautomers (12a, 12'a). Crystallization of a sample from chloroform–hexane gave an almost identical mixture of tautomers (nmr) with mp 165–170°: $[\alpha]_D^{23}$ 157.6° (c 0.33, $CHCl_3$); nmr ($CDCl_3$) 1.25 ppm (t, 3, OCH_2CH_3), 3.65 (s, 3, COOMe), 4.08 and 4.19 (q, total 4, OCH_2CH_3), 4.0 and 4.8–4.9 (m, 6, $C_{1'}H$, $C_{4'}H$, $C_{5'}H_2$ and pyrazoline H's), 5.6 (m, 1, C_3H), 5.86 (dd, 1, J = 3, 6.5, $C_{2'}H$), 7.6 and 8.0 (m, total 15, Ar).

Anal. Calcd. for $C_{34}H_{32}N_2O_{11}$ (644.63): C, 63.35; H, 5.00; N, 4.35
Found: C, 63.18; H, 5.21; N, 4.17

3(5)-Carboethoxy-5(3)-carbomethoxy-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-pyrazole (13a)

(a) A solution of 12a, 12'a (1.0 g, 1.55 mmol) in freshly prepared 0.48 M chlorine in carbon tetrachloride (20 ml) was stored at room temperature for 3 hr and then evaporated to dryness. The residue was dissolved in ether, washed with aqueous sodium bicarbonate and then water, dried and evaporated. The residue was purified from minor by-products by preparative tlc on two 1 m plates using benzene–acetone (9:1) giving 750 mg (75%) of 13a as a homogeneous foam that did not crystallize: λ_{max}^{MeOH} 228 nm (ε 45,400), 273 nm

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(ε 3.27, $CHCl_3$); ν_{max} (film) 1730 cm^{-1}; nmr ($CDCl_3$) 3.68 ppm (s, 3, OMe), 4.64 (m, 3, C_4H, C_5H_2), 4.87 (ddd, 1, $J_{2,4}$ = 1.5 Hz, $J_{3,4}$ ≈ $J_{4,5}$ = 5 Hz, C_4H), 5.47 (dd, 1, $J_{5,6}$ = 5 Hz, C_5H), 5.54 (dd, 1, $J_{5,7}$ = 5 Hz, C_5H'), 6.24 (dd, 1, $J_{2,3}$ = 15.5 Hz, C_2H), 7.06 (dd, 1, C_3H), 7.4 (m, 9, Ar), 7.98 (m, 6, Ar).

Anal. Calcd. for $C_{30}H_{26}O_9$ (530.51): C, 67.92; H, 4.94
Found: C, 67.99; H, 4.98

Methyl *trans*-4,7-anhydro-8-*O*-benzoyl-2,3-dideoxy-5,6-*O*-isopropylidene-D-*allo*-oct-2-enoate (9)

(a) A solution of p-toluenesulfonic acid monohydrate (2.60 g, 13.7 mmol) in acetone (10 ml) was added at 0° to a solution of 1,3-diphenyl-2-(5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-imidazolidine (2.6 g, 5 mmol)[12] in methylene chloride (50 ml). After 20 min the mixture was filtered, the precipitate was washed with methylene chloride and solid sodium bicarbonate was added to the filtrates. After filtration the solution was evaporated to dryness leaving 8[12] as a chromatographically homogeneous (tlc with ether-hexane, 2:1) syrup. The latter was dissolved together with carbomethoxymethylenetriphenylphosphorane (3.3 g, 10 mmol) in methylene chloride (25 ml) and stirred at room temperature for 1 hr. The mixture was then filtered and evaporated leaving a syrup that was chromatographed on a column of silicic acid using ether-hexane (2:1) giving 1.6 g (88%) of chromatographically pure 9 as a clear syrup that was an 8:1 mixture of the *trans* and *cis* isomers by nmr: λ_{max}^{MeOH} 225 nm (ε 16,230), 273 nm (ε 1,000), 280 nm (ε 803); $[\alpha]_D^{23}$ −53.9° (c 0.1, $CHCl_3$); ν_{max} (film) 1732 cm^{-1}; nmr ($CDCl_3$) 1.35 and 1.60 ppm (s, 3, CMe_2), 3.73 (s, 3, OMe), 4.4–4.6 (m, 6, $C_{4-8}H's$), 6.21 (dd, 1, $J_{2,3}$ = 16 Hz, $J_{2,4}$ = 1.5 Hz, C_2H), 7.10 (dd, 1, $J_{3,4}$ = 4.5 Hz, C_3H), 7.6 (m, 3, Ar), 8.15 (m, 2, Ar).

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2-Benzoyloxymethyl-5-(*trans*-carbomethoxymethylene)-furan (10)

The attempted condensation of 2 with trimethyl phosphonoacetate in the presence of potassium *t*-butoxide (as with 8 above) was accompanied by extensive debenzoylation. Following rebenzoylation with benzoyl chloride and pyridine the mixture of products was chromatographed on a column of silicic acid using hexane–ether (5:4). A relatively non-polar product was obtained in low yield and crystallized from chloroform–hexane giving 10 with mp 102–104°: λ_{max}^{MeOH} 229 nm (ε 16,700), 306 nm (ε 24,400); nmr ($CDCl_3$) 3.79 ppm (s, 3, OMe), 5.33 (s, 2, C_6H_2), 6.38 (d, 1, $J_{2,3}$ = 16 Hz, C_2H), 6.56 and 6.62 (d, 1, $J_{3,5}$ = 3.5 Hz, C_3H and C_5H), 7.45 (d, 1, C_3H), 7.53 (m, 3, Ar), 8.12 (m, 2, Ar).

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$\lambda_{max}^{pH\ 2}$ 219 nm (ε 7,200); $\lambda_{max}^{pH\ 12}$ 240 nm (ε 6,900); $[\alpha]_D^{23}$ 14.2° (c 0.2, H_2O); ORD (H_2O) $[\phi]_{256}^{pk}$ 140°, $[\phi]_{240}^{tr}$ 43°; nmr (d_5-pyridine) 3.78 ppm (s, 3, COOMe), 4.21 (dd, 1, J_{gem} = 12 Hz, $J_{4',5'a}$ = 3.5 Hz, $C_{5'a}H$), 4.38 (dd, 1, $J_{4',5'b}$ = 3 Hz, $C_{5'b}H$), 4.66 (~, 1, C_4H), 4.70 (dd, 1, $J_{1',2'}$ = $J_{2',3'}$ = 4 Hz, C_2H), 4.86 (dd, 1, $J_{3',4'}$ = 4 Hz, C_3H), 6.07 (d, 1, C_1H), 6.41 (s, 1, $C_{5(3)}H$).

Anal. Calcd. for $C_{10}H_{14}N_2O_6$ (258.23): C, 46.51; H, 5.47; N, 10.85
Found: C, 45.54; H, 5.50; N, 10.75

3(5)-Carboxamido-4-(β-D-ribofuranosyl)-pyrazole (7c)

(a) A solution of 6 (570 mg, 1 mmol) in saturated methanolic ammonia (70 ml) was stored at room temperature for 5 days and then evaporated to dryness. The residue was partitioned between chloroform and water and the aqueous phase was washed twice with chloroform and then evaporated to dryness leaving 170 mg (72%) of pure, crystalline 7c. An analytical sample from methanol had mp 200–202°: $\lambda_{max}^{pH\ 2}$ 209 nm (ε 7,700); $\lambda_{max}^{pH\ 12}$ 242 nm (ε 7,600); $[\alpha]_D^{23}$ 27.9° (c 0.1, MeOH); ORD (MeOH) $[\phi]_{262}^{pk}$ 1,200°, $[\phi]_{243}^{tr}$ 0°, $[\phi]_{237}^{pk}$ −500°, $[\phi]_{232}^{tr}$ 0°, $[\phi]_{216}^{pk}$ 4,200°; nmr (d_5-pyridine) 4.13 ppm (dd with D_2O, ~, J_{gem} = 11 Hz, $J_{4',5'a}$ = 3.5 Hz, $C_{5'a}H$), 4.29 (dd with D_2O, 1, $J_{4',5'b}$ = 2.5 Hz, $C_{5'b}H$), 4.60 (dd with D_2O, ~, $J_{1',2'}$ = $J_{2',3'}$ = 5 Hz, $C_{2'}H$), 4.7 (m, 2, $C_{3'}H$, C_4H), 5.95 (d, 1, C_1H), 8.22 (s, 1, C_5H), 8.47 (br s, 2, $CONH_2$).

Anal. Calcd. for $C_9H_{13}N_3O_5$ (243.22): C, 44.44; H, 5.39; N, 17.28
Found: C, 44.66; H, 5.32; N, 17.15

(b) A solution of 7a (400 mg) in liquid ammonia was heated in a stainless steel bomb at 100° for 12 hr. Evaporation of the solvent and crystallization from ethanol gave 150 mg (40%) of 7c with mp 200–202° and in all ways identical to that from (a). While the mother liquors appeared to be

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(ε 3,000), 280 nm (ε 2,400); $[\alpha]_D$ −16.5° (c 0.2, $CHCl_3$); nmr ($CDCl_3$) 1.30 ppm (t, 3, OCH_2CH_3), 3.85 (s, 3, COOMe), 4.33 (q, 2, OCH_2CH_3), 5.20 (m, 3, C_4H, C_5H_2), 6.00 (m, 3, C_1H, C_2H, C_3H), 7.35 (~, 9, Ar), 7.95 (m, 6, Ar), 11.4 (vbr, 1, NH).

Anal. Calcd. for $C_{34}H_{30}N_2O_{11}$ (642.60): C, 63.55; H, 4.71; N, 4.36
Found: C, 63.38; H, 4.70; N, 4.35

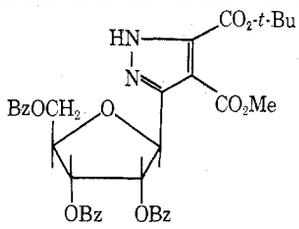
(b) A solution of bromine in methylene chloride was added dropwise at 0° to a solution of 12a, 12'a (1.96 g, 3 mmol) in methylene chloride (100 ml) until an orange color persisted. After a further 15 min the solution was diluted with chloroform, washed with aqueous sodium bicarbonate and water, dried and evaporated. The residue was purified by preparative tlc using chloroform-ethyl acetate (10:3) giving 1.25 g (65%) of 13a identical to that from (a).

3(5)-Carbomethoxy-5(3)-carbo-*t*-butoxy-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyrazoline (12b, 12'b)

A solution of 4 (2.0 g, 3.7 mmol) and *t*-butyl diazoacetate[27] (2.0 g, 14 mmol) in ether (100 ml) was heated under reflux for 7 days. The solvent was evaporated and the residue was purified by preparative tlc using ether-hexane (2:1). In this way 1.19 g (57%) of unreacted 4 was recovered while elution of the more polar product gave 1.08 g (43%) of 12b, 12'b as an amorphous tautomeric mixture containing predominantly two isomers in almost equal amounts. In another, smaller scale experiment this mixture was obtained in 59% yield: λ_{max} 230 nm (ε 34,720), 278 nm (sh, ε 9,230), 283 nm (ε 9,700), 290 nm (sh, ε 8,300); $[\alpha]_D^{23}$ 107.7° (c 0.7, $CHCl_3$); nmr ($CDCl_3$) 1.31 and 1.45 ppm (s, *t*-Bu), 3.68 and 3.81 (s, COOMe).

gen β to the activating group. 1,3-Dipoles such as diazoalkanes, however, have the inherent capacity to exist in mesomeric forms in which the terminal nitrogen rather than carbon is a potential nucleophile. This, together with steric and electronic effects of substituents, allows the possibility that under appropriate conditions the reactions of diazoalkanes and unsaturated compounds can lead to inverse addition such as is found, *e.g.*, in certain reactions of diphenyldiazomethane.[19,26]

In the hope that steric changes alone might, at least in part, lead to such an inverse addition we have examined the reaction of **4** with *tert*-butyl diazoacetate.[27] Should inverse addition occur the product, following dehydrogenation, would be **15**, a type of compound that has previously been prepared by different routes and utilized in the synthesis of formycin B[10] and oxoformycin.[11] The condensation of **4** with *tert*-butyl diazoacetate was slow and even after 7 days under reflux in ether a pyrazoline was obtained in only 43% yield. If, however, one takes into account the recovery of 57% of unreacted **4**, this yield is effectively quantitative. The pyrazoline is clearly a roughly equal mixture of double-bond isomers (presumably **12b** and **12'b** as shown below), since both the methyl and *tert*-butyl ester singlets appeared as twin singlets. Dehydrogenation of these pyrazolines with chlorine gave a homogeneous pyrazole (**13b**) which was isolated in 66% yield by chromatography on silicic acid. The ultraviolet spectrum of this pyrazole was almost identical to that of **13a**, suggesting that the same mode of addition had taken place. In order to confirm this, **13b** was treated with methanolic ammonia at room temperature for 8 days. Under these conditions the major product proved to be the monoamide **16**, the *tert*-butyl ester remaining unchanged. Accordingly, this material was directly treated further with methanolic ammonia at 100° for 48 hr. Under these conditions the crystalline bis(carboxamide) **14** was obtained and shown to be in every way identical with **14** obtained *via* the cycloaddition of **4** with ethyl diazoacetate. In a similar way, direct treatment of **13b** with methanolic ammonia at 100° gave crystalline **14**, although the yield was only 38%. Thus, while, owing to nonquantitative yields, we cannot rule out the possibility of the formation of small amounts of **15** in the above reactions, we



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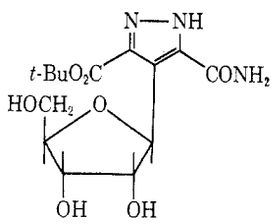

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Anal. Calcd. for $C_{36}H_{36}N_2O_{11}$ (672.65): C, 64.26; H, 5.39; N, 4.17. Found: C, 64.32; H, 5.49; N, 4.05.

3(5)-Carbomethoxy-5(3)-carbo-t-butoxy-4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-pyrazole (13b)

The mixed pyrazolines (**12b**, **12'b**, 750 mg, 1.1 mmol) were dissolved in a freshly prepared 0.47 *M* solution of chlorine in carbon tetrachloride (20 ml) and stored for 2.5 hr at room temperature. The solvent was then evaporated and the residue was dissolved in ether, washed with aqueous sodium bicarbonate and water, dried and evaporated to dryness. Preparative tlc using benzene–acetone (9:1) then gave 500 mg (66%) of **13b** as a homogeneous foam: λ_{max}^{MeOH} 228 nm (ε 48,200), 274 nm (ε 3,000), 281 nm (ε 2,500); $[\alpha]_D^{23}$ -10.4° (*c* 1.0, $CHCl_3$); nmr ($CDCl_3$) 1.49 ppm (s, 9, $O-CMe_3$), 3.84 (s, 3, OMe), 4.7 (m, 3, $C_4'H$, $C_5'H_2$), 5.99 (br s, 3, $C_1'H$, $C_2'H$, $C_3'H$), 7.35 (m, 9, Ar), 7.95 (m, 6, Ar).

Anal. Calcd. for $C_{36}H_{34}N_2O_{11}$ (670.65): C, 64.47; H, 5.11; N, 4.18. Found: C, 64.31; H, 4.92; N, 4.35.

3,5-Dicarboxamido-4-(β-D-ribofuranosyl)-pyrazole (14)

(a) A solution of **13a** (520 mg, 0.96 mmol) in saturated methanolic ammonia (35 ml) was heated in a stainless steel bomb at 100° for 48 hr and then evaporated to dryness. The residue was triturated with hot ethyl acetate to remove benzamide and the solid residue was crystallized twice from water giving 120 mg (44%) of **14** with mp 265-270° (d): $\lambda_{max}^{H_2O}$ 229 nm (sh, ε 8,900); too insoluble for nmr or $[\alpha]_D$; mass spectrum (70 eV, 200°) *m/e* 287 ($M^+ + H$), 183 (Base-CHO + H), 166 (*m/e* 183-NH_3).

Anal. Calcd. for $C_{10}H_{14}N_4O_6$ (286.24): C, 41.96; H, 4.93; N, 19.57. Found: C, 41.79; H, 5.00; N, 19.60.

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(b) The pyrazole **13b** (250 mg) was treated with methanolic ammonia (100 ml) at 100° for 48 hr as in (a) above. After crystallization from water 40 mg (38%) of **14** was obtained with mp (265-270°, d) and infrared spectrum identical to that from (a) above.

3(5)-Carboxamido-5(3)-carbo-t-butoxy-4-(β-D-ribofuranosyl)-pyrazole (16)

A solution of **13b** (500 mg, 0.75 mmol) was dissolved in saturated methanolic ammonia and stored at room temperature for 8 days. Following evaporation of the solvent the residue was partitioned between water and chloroform and the aqueous phase was evaporated to dryness. The residue was purified by preparative tlc using chloroform–methanol (7:3) giving 140 mg (55%) of **16** as a homogeneous foam: nmr (d_5-pyridine) 1.49 ppm (s, 9, $OCMe_3$), 4.15 (dd, 1, J_{gem} = 12 Hz, $J_{4',5'a}$ = 3 Hz, $C_{5'a}H$), 4.32 (dd, 1, $J_{4',5'b}$ = 3 Hz, $C_{5'b}H$), 4.50 (m, 1, $C_4'H$), 4.96 (dd, 1, $J_{2',3'}$ = 7 Hz, $J_{3',4'}$ = 3.5 Hz, $C_3'H$), 5.15 (dd, 1, $J_{1',2'}$ = 7 Hz, $C_2'H$), 6.37 (dd, 1, $C_1'H$), 8.52 and 8.85 (br s, 1, NH_2).

Treatment of this material (140 mg) with saturated methanolic ammonia at 100° for 48 hr followed by evaporation of the solvent and crystallization from water gave 60 mg (52%) of **14** that was in all ways identical to that described above.

Methyl 4,7-anhydro-8-O-benzoyl-2-bromo-5,6-O-isopropylidene-2,3-dideoxy-D-*allo*-oct-2-enoate (17)

A solution of **8** (regenerated from its 1,3-dipnenylimidazolidine derivative, 4.0 g, 8.0 mmol using *o*-toluenesulfonic acid[12] and bromocarbomethoxymethylenetriphenylphosphorane (3.25 g, 7.9 mmol)[29] in methylene chloride (150 ml) was stored at room temperature for 4 hr. The solution was then washed with water, dried ($MgSO_4$) and evaporated leaving a residue that was chromatographed on a column of silicic acid. Elution with ether–hexane (2:1) gave 2.25 g (65%) of **17** with mp 69-72°: λ_{max}^{MeOH} 230 nm (ε 21,000), 273 nm (ε 1,200), 281 nm (ε 900); $[\alpha]_D^{23}$ -47.6° (*c* 0.17, $CHCl_3$); nmr ($CDCl_3$) 1.36 and 1.59 ppm (s, 3, CMe_2), 3.70 (s, 3, OMe), 4.46 (br s, 3, C_2H, C_8H_2), 4.71 (m, 3, C_5H, C_6H), 4.93 (dd, 1, $J_{3,4}$ = 7 Hz, $J_{4,5}$ = 2.5 Hz, collapsing to doublet upon irradiation of C_3H), 7.29 (d, 1, C_3H), 7.4 (m, 3, Ar), 8.0 (m, 2, Ar).

Anal. Calcd. for $C_{19}H_{21}O_7Br$ (441.28): C, 51.71; H, 4.80. Found: C, 51.68; H, 4.81.

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3-Carbomethoxy-4-(5-O-benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-2-pyrazoline (11)

A solution of **9** (100 mg, 0.28 mmol) and diazomethane (~1.5 mmol) in ether (20 ml) was stored at 0° for 2 hr and then evaporated to dryness leaving 100 mg (90%) of **11** as a chromatographically homogeneous white foam. Upon storage, **11** gradually developed a faster moving impurity (cyclopropane?) and for analytical purposes the material was purified by preparative tlc using chloroform–methanol (19:1). Elution of the major product gave chromatographically homogeneous **11** as a white foam, the nmr spectrum of which indicated the presence of a mixture of isomers: λ_{max}^{MeOH} 229 nm (ε 14,200), 282 nm (ε 3,800), 297 nm (ε 3,900); $[\alpha]_D^{23}$ -21.2° (*c* 0.8, $CHCl_3$).

Anal. Calcd. for $C_{20}H_{24}N_2O_7$ (404.43): C, 59.40; H, 5.98. Found: C, 59.28; H, 6.02.

3(5)-Carbomethoxy-4-(5-O-benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-pyrazole (18)

A solution of **17** (250 mg, 0.56 mmol) and diazomethane (~1.25 mmol) in ether (35 ml) was stored at 0° for 2 hr and then evaporated to dryness leaving the pyrazoline (**18**) as a chromatographically homogeneous, unstable foam in quantitative yield. This residue was chromatographed on a column of silicic acid using ether–hexane (2:1) which led to essentially complete conversion to **19**. To remove traces of highly polar impurities the crude **19** was further purified by preparative tlc using ether–hexane (2:1) giving 120 mg (57%) of **19** with mp 129-130° from ether–hexane: λ_{max}^{MeOH} 228 nm (ε 18,400), 274 nm (ε 1,000), 281 nm (ε 1,000); $[\alpha]_D^{23}$ 15.3° (*c* 0.5, $CHCl_3$); nmr ($CDCl_3$) 1.36 and 1.63 ppm (s, 3, CMe_2), 3.88 (s, 3, OMe), 4.3-4.7 (m, 3, $C_4'H$, $C_5'H_2$), 4.75 (narrow m, 2, $C_2'H$, $C_3'H$), 5.44 (narrow m[39], 1, $C_1'H$), 7.45 (m, 3, Ar), 7.71 (s, 1, $C_5(3)H$), 8.02 (m, 2, Ar).

JOC-21-13

Anal. Calcd. for $C_{20}H_{22}N_2O_7$ (402.42): C, 59.69; H, 5.51; N, 6.96. Found: C, 59.83; H, 5.52; N, 6.71.

3,5-Di-O-benzoyl-1,2-O-[α-(2-carbomethoxyethynyl)-benzylidene]-α-D-ribofuranose (23)

Concentrated ammonium hydroxide was added dropwise to a solution of silver nitrate (1.1 g, 6.5 mmol) in water (20 ml) until the initial brown precipitate dissolved. This solution was cooled to 0° and to it was added a solution of methyl propiolate (487 mg, 5.8 mmol) in acetone (10 ml). Water (100 ml) was then added giving a white precipitate that was collected, washed with water, and dried *in vacuo* over P_2O_5 giving 1.1 g (quant.) of silver methyl propiolate. The latter and 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide (from 5.0 mmol of the 1-O-acetate) were reacted in methylene chloride (50 ml) for 48 hr at room temperature as above. The crude product, which contained one major spot and some more polar impurities, was chromatographed on a column of silicic acid using a gradient of 5-20% ethyl acetate in hexane giving 1.3 g (50%) of pure **23** as a clear syrup: λ_{max}^{MeOH} 229 nm (ε 30,000), 274 nm (ε 2,200), 281 nm (ε 1,800); $[\alpha]_D^{23}$ 71.4° (*c* 1.0, $CHCl_3$); nmr ($CDCl_3$) 3.75 ppm (s, 3, OMe), 4.42 (dd, 1, J_{gem} = 13 Hz, $J_{4',5'a}$ = 4 Hz, $C_{5'a}H$), 4.51 (dd, 1, $J_{4',5'b}$ = 4.5 Hz, $C_{5'b}H$), 4.6 (~, 1, $C_4'H$), 5.13 (dd, 1, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 8 Hz, $C_3'H$), 5.27 (dd, 1, $J_{1',2'}$ = 4 Hz, $C_2'H$), 6.20 (d, 1, $C_1'H$), 7.2-7.55 (m, 9, Ar), 7.6-7.8 (m, 2, Ar), 7.98 (m, 4, Ar).

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Anal. Calcd. for $C_{30}H_{24}O_9$ (528.52): C, 68.18; H, 4.58. Found: C, 67.94; H, 4.78.

3,5-Di-O-benzoyl-1,2-O-[α-(3-carbomethoxypyrazol-4-yl)-benzylidene]-α-D-ribofuranose (25)

A solution of **23** (1.3 g, 2.5 mmol) and diazomethane (5 mmol) in ether (30 ml) was stored at 0° for 1 hr and then evaporated to dryness. The residue was chromatographed on a column of silicic acid using a gradient of 0-3% methanol in chloroform and giving 661 mg (47%) of **25** as a clear syrup[40]: λ_{max}^{MeOH} 230 nm (ε 31,400), 274 nm (ε 2,000), 281 nm (ε 1,600); $[\alpha]_D^{23}$ 110.1° (*c* 1.0, $CHCl_3$); nmr ($CDCl_3$) 3.66 ppm (s, 3, OMe), 3.80 (m, 1, $C_4'H$), 4.24 (dd, 1, J_{gem} = 12 Hz, $C_{5'a}H$), 4.49 (dd, 1, $J_{4',5'b}$ = 3.5 Hz, $C_{5'b}H$), 4.96 (dd, 1, $J_{2',3'}$ = 5.5 hz, $J_{3',4'}$ = 9 Hz, $C_3'H$), 5.31 (dd, 1, $J_{1',2'}$ = 4 Hz, $C_2'H$), 6.21 (d, 1, $C_1'H$), 7.06 (s, 1, C_5H), 7.2-7.7 (m, 11, Ar), 7.95 (m, 4, Ar).

Anal. Calcd. for $C_{31}H_{26}N_2O_9$ (570.54): C, 65.26; H, 4.59; N, 4.91. Found: C, 65.40; H, 4.67; N, 4.72.

1,2-O-[α-(3-carbomethoxypyrazol-4-yl)-benzylidene]-α-D-ribofuranose (28)

A solution of **25** (200 mg, 0.35 mmol) in methanol (20 ml) was treated for 20 hr at room temperature with 0.75 mmol of sodium methoxide and then neutralized with Dowex 50 (H^+) resin. The evaporated filtrate was purified by preparative tlc using chloroform–methanol (85:15) to give 60 mg (50%) of **28** as a foam that did not crystallize: λ_{max}^{MeOH} 229 nm (sh, ε 4,400); $[\alpha]_D^{23}$ 38.3° (*c* 0.8, MeOH); nmr (d_6DMSO) 3.52 ppm (s, 3, OMe), 3.6 (~, 4, $C_2'H$, $C_3'H$, $C_5'H_2$), 4.42 (dd, 1, $J_{1',2'}$ = 4 Hz, $C_2'H$), 4.63 and 5.15 (m, 1, OH), 5.82 (d, 1, $C_1'H$), 7.2-7.4 (m, 3, Ar), 7.4-7.6 (m, 2, Ar), 7.76 (s, 1, C_5H).

JOC-21-15

Anal. Calcd. for $C_{17}H_{18}N_2O_7$ (362.33): C, 56.35; H, 5.01; N, 7.73. Found: C, 56.46; H, 5.12; N, 7.91.

4-Benzoyl-3-carbomethoxypyrazole (29)

A solution of **25** (130 mg) in 90% trifluoroacetic acid (1 ml) was stored at room temperature for 2.5 hr and then evaporated to dryness *in vacuo*. The residue was purified by preparative tlc using chloroform–methanol (97:3) giving a single band (a mixture of **29** and the sugar fragment) which crystallized from ethyl acetate–hexane to give 20 mg (40%) of **29** with mp 131-132° (reported[28] mp 129°). No further crystals could be obtained from the mixture: λ_{max}^{MeOH} 252 nm (ε 14,900); nmr ($CDCl_3$) 3.64 ppm (s, 3, OMe), 7.50 (m, 3, Ar), 7.84 (m, 2, Ar), 8.16 (s, 1, C_5H). Mass spectrum (70 eV) *m/e* 230 (M^+), 171 ($M-CO_2Me$), 153 ($M-C_6H_5$).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$ (230.22): C, 62.60; H, 4.38; N, 12.17. Found: C, 62.19; H, 4.36; N, 11.85.

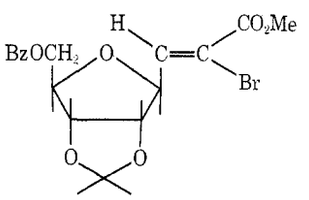
Treatment of **5** under comparable conditions led to no change.

[39] Presumably due to virtual coupling with C_3H.

[40] The low recovery is difficult to understand since tlc of the crude mixture showed only traces of impurities.

can provide no positive evidence for the inverse addition reactions under these conditions.

We mentioned above that the dehydrogenation of the 2′,3′-*O*-isopropylidene protected 2-pyrazoline (**11**) was not readily accomplished by the methods used successfully on the tribenzoate **5**. The desired pyrazole **19** could, however, be prepared by a different route.[28] Thus reaction of the aldehyde **8** with bromocarbomethoxymethylenetriphenylphosphorane[29] in methylene chloride gave the crystalline bromo olefin **17** in 65% yield. The stereochemistry of **17** is assumed to be as shown, both owing to analogy with the known trans configurations of **4** and **9** and to the very similar chemical shifts of the C_3 protons in all three compounds. Since the cis deshielding parameter of bromine is roughly 0.5 ppm smaller than that of the carbomethoxy group, one would expect C_3 H in the isomer of **17** in which H and Br are cis to be at markedly higher field.[30] Cycloaddition of diazomethane and **17** led quantitatively to a bromopyrazoline (probably **18**) which was too unstable to purify in any way, and underwent dehydrobromination to the pyrazole **19** on brief heating in chloroform, washing with aqueous sodium bicarbonate, or passage through a column of silicic acid. Using the latter method, crystalline 3(5)-carbomethoxy-4-(5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrazole (**19**) was obtained in 57% yield from **17**.



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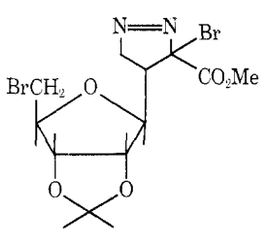

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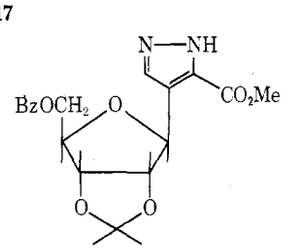

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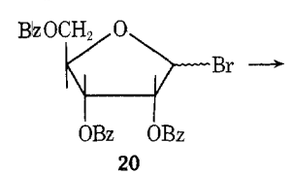
Finally, it also seemed feasible to directly prepare pyrazole *C*-glycosides *via* direct cycloaddition of diazo compounds to ribosylacetylenes. Such a method has been used in the glucopyranose series[17] and its application appears to have been limited by the relative inaccessibility of furanosylalkynes. While a few pyranosylalkynes have been known for many years,[31] the first furanosyl analog has only recently been described.[32] In an effort to prepare the desired methyl 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)propiolate (**24**) we have investigated the condensation of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**20**) with the silver derivative of methyl propiolate **22**.[33] A facile reaction took place with separation of silver bromide and formation of one major product in addition to several minor, more polar by-products. The major product was isolated in 50% yield by chromatography and shown to have the expected elemental analysis for the desired ribofuranosylacetylene **24**. The nmr spectrum of this product, however, was somewhat unusual, since the anomeric proton appeared as a doublet ($J_{1',2'}$ = 4 Hz) at 6.20 ppm. This position is reminiscent of *N*-glycosides (nucleosides) and many carbohydrate 1,2-acetals but is considerably downfield from where one would expect to find $C_{1'}$ H in **24**, since both a number of *C*-glycosyl nucleosides[34] and acetylenic carbinols[35] show the related protons at roughly 5 ppm.[36] In addition, $C_{2'}$ H and $C_{3'}$ H appeared as doublets of doublets at 5.27 and 5.13 ppm, both roughly 0.5 ppm upfield of these protons in a variety of benzoylated nucleosides and glycosides. Nevertheless, this product was directly treated with diazomethane to afford an analytically pure pyrazole which was not the previously described compound **6**. Once again, the nmr spectrum of this substance showed the anomeric proton as a doublet at 6.21 ppm and $C_{2'}$ H and $C_{3'}$ H as doublets of doublets at 5.31 and 4.96 ppm. These chemical shifts are quite unlike those of the pyrazole **6**, in which $C_{1'}$ H, $C_{2'}$ H, and $C_{3'}$ H all appeared at 5.80 ppm.

On the basis of these results we propose that the condensation of **20** and silver methyl propiolate does not give the ribofuranosylacetylene **24** but rather 3,5-di-*O*-benzoyl-1,2-*O*-[α-(2-carbomethoxyethynyl)benzylidene]-α-D-ribofuranose (**23**) arising from alkylation of the intermediate 1,2-benzoxonium ion **21**. The subsequent product from addition of diazomethane to **23** would then be the pyrazole **25** rather than **6**. The formation of **23** finds close analogy in the isolation by Hanessian and Pernet[37] of a similar α-substituted 1,2-*O*-ethylidene-α-D-glucopyranose upon attempted alkylation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl chloride with sodio diethylmalonate.



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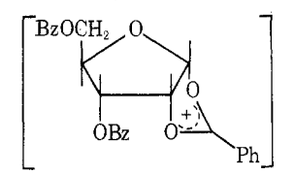

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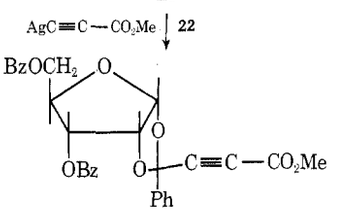

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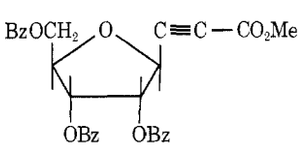

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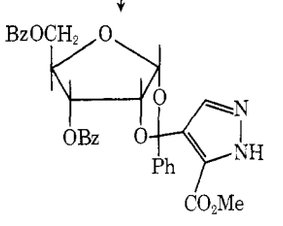

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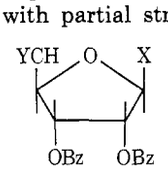
Support for these assignments comes from both spectroscopic and degradative studies. Firstly, an examination of the nmr spectra in deuteriochloroform of over 30 compounds with partial structure **26** (both *O*- and *N*-glycosides and in both the pentose and hexose series) indicated that the chemical shifts of $C_{2'}$ H vary between 5.56 and 6.40 ppm while those of $C_{3'}$ H are found at 5.55–6.25 ppm. On the other hand, nine differently substituted compounds of formula **27** showed $C_{2'}$ H at 4.92–5.08 ppm, and $C_{3'}$ H at 4.60–5.25 ppm. While deshielding of $C_{2'}$ H in



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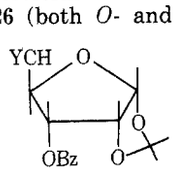

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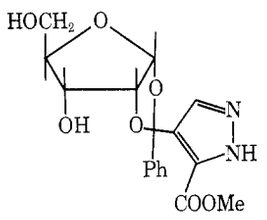
compounds of type **26** is entirely to be expected due to the effect of the 2′-*O*-benzoyl group, it is not immediately obvious why $C_{3'}$ H in 1,2-*O*-acetals (**27**) should appear at roughly 1 ppm higher field than the corresponding proton in **26**. Regardless of whether this is a consequence of steric, conformation, or other effects, it is clear that the high-field chemical shifts of $C_{2'}$ H and $C_{3'}$ H in both **23** and **25** is consistent with the 1,2-*O*-acetal rather than the 2,3-dibenzoyl structures.

It might also be pointed out that **23** and **25** have the typically large values of $J_{3',4'}$ (8 and 9 Hz) shown by compounds related to **27** and indicative of the very small dihedral angle between $C_{3'}$ H and $C_{4'}$ H in these conformationally rigid molecules.

In addition, it might be noted that the chiral α-substituted benzylidene function in **23** and **25** allows the possibility of two diastereoisomers. The observed sharp nmr spectra, however, suggest that only one isomer is formed. Since the intermediate benzoxonium ion **21** is highly hindered on one face by the furanose ring and, in particular, the 3′-*O*-benzoyl group, it is not surprising that addition of the acetylide occurs stereoselectively from the unhindered exo face.

Prolonged treatment of **25** with methanolic sodium methoxide under conditions that are known to completely debenzoylate nucleosides gave, as expected, the diol **28**, clearly showing that the benzoyl ester originally present in **20** had been converted into a base-stable function. The nmr spectrum of **28** showed the presence of a single phenyl group which was clearly not a benzoyl group since there were no signals at 8.0 ppm due to the protons ortho to the carbonyl function. Finally, treatment of **25** with 90% trifluoroacetic acid at room temperature led to quite rapid cleavage of the 1,2-*O*-acetal function, giving 4-benzoyl-3-carbomethoxypyrazole (**29**). The latter could, unfortunately, not be separated from the other reaction product, presumably 3,5-di-*O*-benzoyl-D-ribofuranose, by tlc in a variety of solvents. By direct crystallization, however, **29** was obtained in crystalline form in 40% yield. This compound has previously been synthesized by Bastide and LeMatre[38] using an independent route and its isolation completes and confirms the characterization of **23** and **25**.



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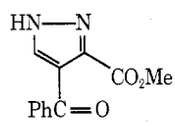

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From the above it is clear that the preparation of β-D-ribofuranosylacetylenes bearing participating groups such as benzoyl esters at $C_{2'}$ is not of practical importance as a route to *C*-glycosyl pyrazoles. Related work is, however, being pursued by Drs. H. Ohrui, R. S. Klein, and J. J. Fox at the Sloan Kettering Institute for Cancer Research using 2,3-*O*-isopropylidene-D-ribofuranose derivatives and will be reported at a later date. We are grateful to Drs. Ohrui and Fox for a discussion of our respective activities and for their advice.

Registry No.—**2**, 39037-99-5; **4**, 51424-91-0; **5**, 50720-80-4; **6**, 51424-92-1; **7a**, 51424-93-2; **7b**, 51424-94-3; **7c**, 51424-95-4; **8**, 39037-13-3; *cis*-**9**, 51424-96-5; *trans*-**9**, 51424-97-6; **10**, 51424-98-7; **11** *R* isomer, 51424-99-8; **11** *S* isomer, 51425-00-4; **12a**, 51472-51-6; **12b**, 51425-01-5; **13a**, 51425-02-6; **13b**, 51425-03-7; **14**, 50720-87-1; **16**, 51425-04-8; **17**, 51425-05-9; **19**, 51425-06-0; **23**, 51425-07-1; **25**, 51425-08-2; **28**, 51425-09-3; **29**, 19867-49-3; *p*-toluenesulfonic acid, 104-15-4; 1,3-diphenyl-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazolidine, 39038-02-3; 1,3-diphenyl-2-(5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazolidine, 39037-12-2; trimethyl phosphonoacetate, 26583-90-4; diazomethane, 334-88-3; ethyl diazoacetate, 623-73-4; *tert*-butyl diazoacetate, 35059-50-8.

Miniprint Material Available. Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprinted and supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2176.

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Reactions of 2-Acyloxyisobutyryl Halides with Nucleosides. V. Reactions with Cytidine and Its Derivatives[1]

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The reaction of cytidine with 2-acetoxyisobutyryl chloride in acetonitrile at 80° leads to the isolation in good yield of 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)cytosine hydrochloride (**4a**). By conducting the reaction at room temperature an intermediate 5′-*O*-(trimethyldioxolanone) ether (**5**) is obtained and can be cleaved to **4a** in very high yield. Under different conditions of hydrolysis **5** can be efficiently converted into either 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine hydrochloride or 1-(β-D-arabinofuranosyl)cytosine. A variety of base analogs of cytidine have also been treated with 2-acetoxyisobutyryl chloride to give related analogs of **4a**. The reaction can also be extended to other acyl derivatives, since cytidine and 2-butyryloxyisobutyryl chloride give 2,2′-anhydro-1-(3′-*O*-butyryl-β-D-arabinofuranosyl)cytosine hydrochloride in good yield.

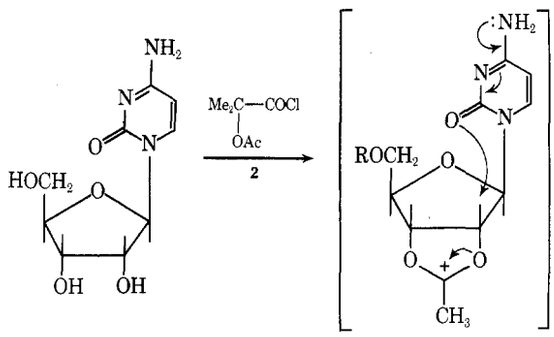
Previous papers in this series have outlined the anomalous reactions of 2-acetoxyisobutyryl halides with uridine,[1,4] adenosine,[5] and several adenosine analogs.[6] In all cases the observed products could be explained *via* the conversion of the 2′,3′-cis diol function to a reactive 2′,3′-acetoxonium ion.[4] In the case of the purine nucleosides[5-7] such acetoxonium ions are opened by attack of halide ion to form isomeric 2′,3′-trans chloro acetates with the 2′-*O*-acetyl-3′-deoxy-3′-halo-β-D-xylofuranosyl isomer predominating. In the uridine series, however, the acetoxonium ion undergoes preferential intramolecular attack by the C_2 carbonyl group of the pyrimidine ring to initially form 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil, which is then opened by halide ion giving a 3′-*O*-acetyl-2′-deoxy-2′-halouridine derivative with overall retention of configuration.

In the cytidine series one might expect a similar type of participation by the C_2 carbonyl of the cytosine ring, and in this paper we describe some of the reactions of cytidine and several cytidine derivatives and analogs with 2-acetoxyisobutyryl chloride.

The addition of an excess of 2-acetoxyisobutyryl chloride (**2**) to a suspension of cytidine (**1**) in acetonitrile at 80° led to the formation of a clear solution within about 5 min. On continued heating, a crystalline product began to separate and after a total of 30 min the remaining material was precipitated with ether. Crystallization of the residue from methanol–acetone then gave crystalline 2,2′-anhydro-(3′-*O*-acetyl-β-D-arabinofuranosyl)cytosine hydrochloride (**4a**) in 68% yield. The structure of **4**, which undoubtedly arises *via* the 2′,3′-acetoxonium ion (**3**), was apparent from its analytical and spectroscopic properties. Thus the ultraviolet spectrum of **4a** showed double maxima at 231 and 263 nm typical of the 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine (**4b**) chromophore.[8] The presence of a single acetyl group was indicated by nmr spectroscopy and this function was located at $C_{3'}$ by the 0.9-ppm downfield shift of C_3 H relative to that in **4b**. Further confirmation of this structure *via* chemical degradation to **4b** will be presented later in this paper.

Our interest in **4a** became acute with the observation that this substance showed pronounced activity against several DNA viruses in tissue culture and against L-1210 leukemia in mice.[9] Subsequent to this aspect of our work several new methods for the synthesis of **4b** have been described[10] and this compound has been the subject of extensive examination as an antitumor agent of low toxicity.[11] In addition, there has been interest in the pharmacological properties of the related 3′-phosphate ester (**4c**).[12]

While the preparation of **4a** described above was quite efficient and simple on a modest scale, attempted scale up to a 100-mmol level led to reduced yields of crystalline material. This was largely due to the formation of by-products, the major ones being tentatively identified as cytosine nucleosides containing chlorinated sugars. It remains uncertain whether these products arise by direct opening of **3** with halide ion, or by further reactions of **4a**.



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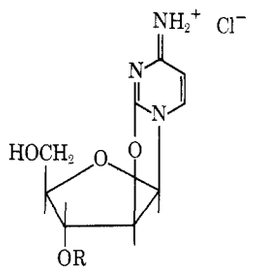

4a, R = $COCH_3$
b, R = H
c, R = PO_3H_2