Nucleosides XCVII. Synthesis of an 8-(D-Ribofuranosyl)pyrazolo[1,5-*a*]-1,3,5-triazine. A New Type of *C*-Nucleoside (1)

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Sir:

Recent reports (2-4) from our laboratory have described the synthesis of two new types of intermediates useful for the preparation of a number of *C*-nucleosides. Ribofuranosyl acetylenic esters **1** have been utilized for the synthesis of triazole and pyrazole *C*-nucleosides (2) and of 6-β-D-ribofuranosylpyrimidines (3) while ethyl 2-(D-ribofuranosyl)-2-formylacetate (**2**) (4) was transformed to 5-(β-D-ribofuranosyl)isocytosine (an amino analogue of pseudouridine) that has exhibited antileukemic activity in preliminary studies.

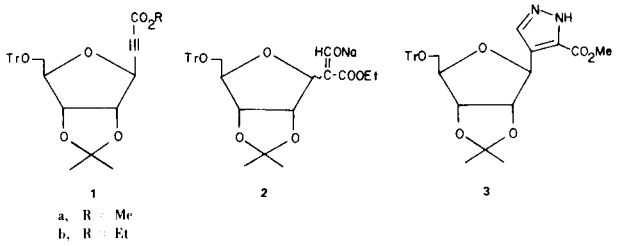
We wish to report here the utilization of **1a** and **9** (the latter structurally related to **2**) for the synthesis of an 8-D-ribosylated derivative of a pyrazole[1,5-*a*]-1,3,5-triazine (**5**), a new type of *C*-nucleoside and a potentially important precursor of analogues of the formycins (6).

A key intermediate in this synthesis is the ribosylated aminopyrazole **10**, obtained by two different and convergent routes. One route utilizing 2-(D-ribofuranosyl)-2-methoxymethylenecacetonitrile (**9**) was expected to give an anomeric mixture of the desired products **10** and **11**. The somewhat longer sequence *via* **3** (2) (obtained from **1a** in one step) was expected to afford the pure β anomer **10**, as **3** itself was anomerically pure, thus allowing a direct confirmation of the anomeric assignment of the pair of anomers obtained from **9**. Experimentally, however, both routes afforded a mixture of anomers (*vide infra*).

Treatment of **3** with an excess of anhydrous hydrazine in ethanol overnight afforded, after crystallization, the hydrazide **4** (92%) m.p. 192-193°. Nitrosation of **4** with sodium nitrite and aqueous hydrochloric acid in acetone at 0-5° for 20 minutes afforded the acyl azide **6** as a major product, ir (chloroform): 2150 (N_3); 1670 cm^{-1} (C=O). Heating crude **6** in refluxing ethanol for 3 hours afforded, after purification by dry column chromatography, the carbamate **8** (44.5% from **4**) which was isolated as a syrup. Carbamate **8** was hydrolyzed to the corresponding aminopyrazole upon treatment with sodium hydroxide in a 2:1 water-ethanol mixture heated to reflux for 5 hours. This reaction was accompanied unexpectedly by epimerization, thus affording, after chromatographic separation, the β-anomer **10** (syrup, 21.5%) and the α-anomer **11** (crystalline, 40%, m.p. 102-106°). Both **10** and **11** anomerize in both aqueous and non aqueous solvents, even in neutral conditions.

The same anomers **10** and **11** were also obtained by the following alternate procedure. A mixture of **5** (7) and ethyl formate was treated with sodium ethoxide in anhydrous ether at room temperature for 15 hours to give, after evaporation of solvent *in vacuo*, the sodium enolate **7**.

Chart I

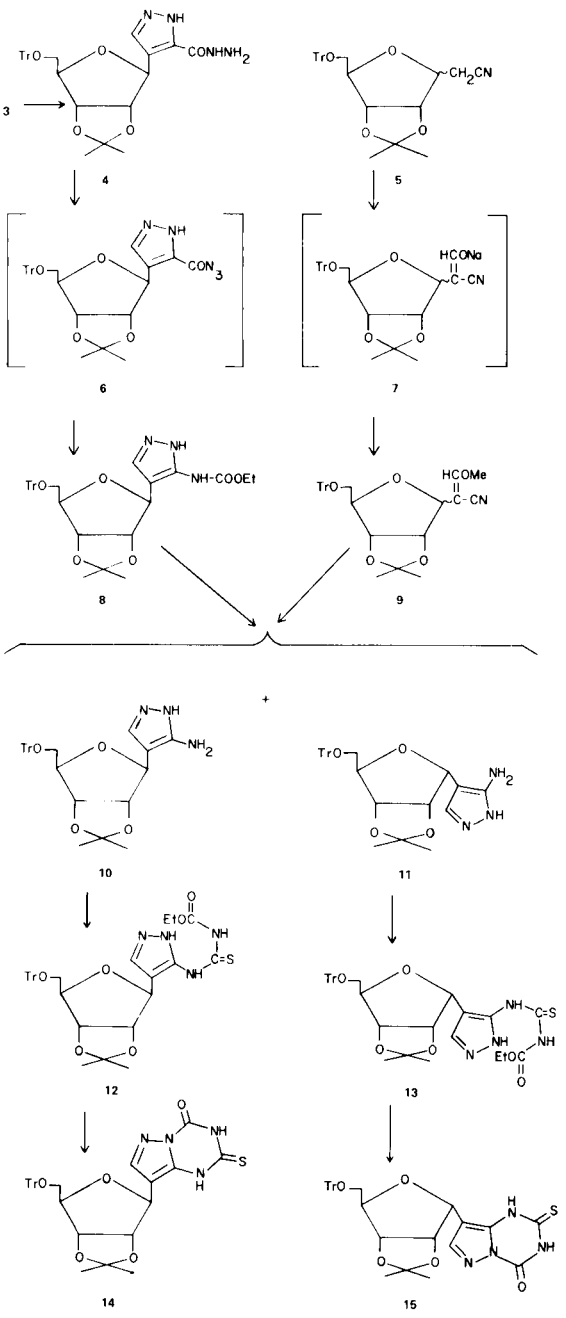


1 (a, R = Me; b, R = Et) 2 3

Treatment of **7** with methyl iodide in DMF for 5 hours at room temperature afforded, after chromatography on silica gel, a 40% yield of the methyl vinyl ether **9**, ir (potassium bromide): 2210 (CN), 1640 and 1250 cm^{-1} (C=C-O-). The pmr spectrum indicated that the product isolated was anomerically pure although no assignment of configuration or of stereochemistry of the double bond could be made. The crude material **9** obtained from the methylation step was cyclized satisfactorily by refluxing it for 15 hours in anhydrous hydrazine in the presence of sodium ethoxide to afford, after separation by chromatography on silica gel, the same aminopyrazoles **10** (12% overall yield from **5**) and **11** (18% yield from **5**).

Treatment of a solution of the aminopyrazole **10** (or **11**) in acetonitrile with an acetonitrile solution of SCN-COOEt

Chart 2



at 0° for 3 hours afforded, after chromatography, a good yield of **12** (or **13**). Cyclization of these intermediates to the pyrazolotriazine *C*-nucleoside **14** (or **15**) occurred very rapidly upon treatment of a methanolic solution of **12** (or **13**) with 1*N* sodium hydroxide. After customary work-up and purification by chromatography on silica gel the pure product **14** (or **15**) was obtained in excellent yield. The α anomer **15** crystallized from diethyl ether m.p. 156-157°. As expected, the uv spectra of compounds **14** and **15** are quite similar to that of 4-oxo-2-thioxopyrazolo[1,5-*a*]-1,3,5-triazine (8).

The configurational assignments for nucleosides **10**, **12** and **14** as β and for nucleosides **11**, **13** and **15** as α are based on the pmr data for these compounds (see Table I). The chemical shift of H-1′ for the α-anomer in any anomeric pair (**10**,**11**), (**12**,**13**) and (**14**,**15**) occurs at lower field than that for the corresponding β-anomer (9). Furthermore, the difference of chemical shifts of the two isopropylidene methyl signals (Δδ) for an α-anomer is in all cases smaller than that for the corresponding β-anomer, although their values may be larger than those predicted for the α-anomers of *N*-nucleosides (10, 11).

Proper elemental analyses have been obtained for compounds **4**, **8**, **9**, **10**, **11**, **14** and **15**.

Further studies on the application of these synthetic approaches are underway in this laboratory.

Table I

Pmr data (a) for compounds **4**, **8-15** at 100 MHz with TMS as internal standard

Compound	Solvent	(δ)H-1′	$J_{1',2'}$	$CMe_2\Delta\delta$
4	$DMSOd_6$	5.41	3.3	0.23
8	$DMSOd_6$	4.86	4.0	0.20
8	deuteriochloroform	4.95	4.2	0.24
9	deuteriochloroform	4.25	4.6	0.22
10	deuteriochloroform	4.76 (b)	(b)	0.22
11	deuteriochloroform	5.15	2.2	0.19
12	deuteriochloroform	5.00	4.6	0.23
13	deuteriochloroform	5.43	3.1	0.09
14	deuteriochloroform	4.92	5.0	0.25
15	deuteriochloroform	5.23	2.7	0.24

(a) Chemical shifts in ppm, coupling constants in Hz. (b) In a non-resolved multiplet including H-2′ and H-3′.

REFERENCES AND NOTES

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(11) The same criteria have been applied by Moffatt, *et al.*, in Reference 7 for anomeric assignment to a number of *C*-glycosyl derivatives.