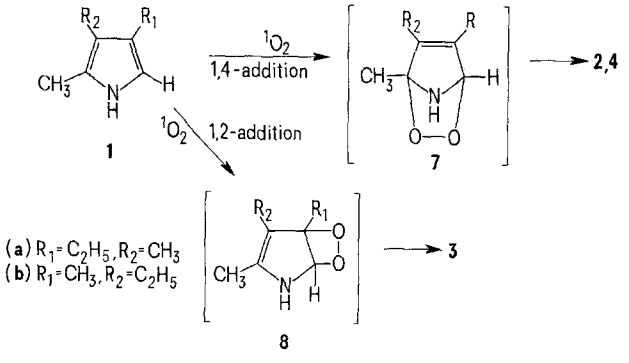
step in the formation of *2* and *4* (Scheme). There are several examples of this type of behavior[2,9,10,12], and two possible mechanistic routes have been considered[12]. The details of the formation of hydroxylactam *3* are less obvious. Presumably a dioxetane intermediate (*8*)[2,10] is implicated; however, whether it is formed directly from attack of $^1O_2$ on *1* or by rearrangement of *endo*peroxide *7* is unclear. As expected, only *3b* and *4b* are obtained when the photooxidation of *1b* is carried out in chloroform solvent.

All photoproducts *2–4* are extremely acid labile. For example, hydroxylactam *3b* converts to *4b* in H_3O^+,



and *2b*, *3b* and *4b* all convert to the weakly fluorescent exomethylene compound *6b* in an aprotic solvent with acid catalysis. It is of special interest to note that *6b* does not undergo photooxygenation to *5*. Further work on the mechanistic details of these reactions and solvent and mechanism studies on the photooxidation of krypto- and hemopyrrole are under investigation in our laboratories.

Zusammenfassung. Die durch Rose Bengal sensibilisierte Photooxydation des Hemopyrrols in Methanol ergab 3-Äthyl-5-methoxy-4, 5-dimethyl-3-pyrrolin-2-on, 3-Äthyl-3-hydroxy-4, 5-dimethyl-4-pyrrolin-2-on und 3-Äthyl-5-hydroxy-4, 5-dimethyl-3-pyrrolin-2-on.

D. A. LIGHTNER[13], R. D. NORRIS, D. I. KIRK and R. M. KEY

Department of Chemistry, Texas Tech University, P.O. Box 4260, Lubbock (Texas 79409, USA), 20 November 1973.

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[13] The authors wish to thank the National Science Foundation (GP-35699X) and the National Institute of Child Health and Human Development (HD-07358) for generous support of this work. We thank Mr. JORDAN HODGE for determining all mass spectra reported in this work.

Imidazole Nucleoside Analogues Possessing a Non-Glycosidic Link between Sugar and Base

A number of analogues of most of the important naturally occurring imidazole ribofuranosides have been prepared[1,2,3] for use in studies of the *de novo* biosynthesis of purines and as potential anti-virus and anti-cancer compounds. Most of them have the same carbohydrate component as the natural purine precursors and all contain a glycosidic link between sugar and base. Recently[4] we synthesized an imidazole nucleoside (I) in which the heterocyclic ring is connected to the 2'-position of the sugar. Compounds of this class should be stable in the presence of glycoside-splitting enzymes and might be expected to be useful metabolic inhibitors; however, the examples we reported are stereochemically dissimilar to the natural ribofuranosides. Our work has now been extended to provide nucleoside analogues that are more closely related to the key purine precursor AICAR and the corresponding nucleoside (II) or which are capable of attaining a similar conformation during interactions with enzymes. One example is the altropyranoside derivative (III) which has similar dimensions to AICAR particularly

Table I. Stereochemical comparison of nucleoside analogue (III) with the naturally occurring nucleoside (II) corresponding to AICAR. Interatomic distances between various atoms were measured on Dreiding stereomodels

Analogue (III) (in boat confirmation)		Nucleoside (II)	
Atoms	Distance (Å) apart	Atoms	Distance (Å) apart
C_5–N_1	3.60	C_6–N_2	3.48
C_4–C_1	2.44	C_5–C_2	2.74
N_1–O_3	4.48	N_2–O_4	4.25
N_1–O_2	3.56	N_2–O_3	3.56
O_5–C_1	1.43	O_6–C_2	2.36
O_5–N_2	2.44	O_6–N_2	2.80
O_5–C_2	2.52	O_6–C_3	2.88
O_5–C_3	2.52	O_6–C_4	2.40
C_4–C_2	2.52	C_5–C_3	2.52
C_4–O_2	3.44	C_5–O_3	3.80
C_4–N_1	3.16	C_5–N_2	3.60

Table II. T.l.c. data for various nucleoside analogues

	RF value on cellulose thin layers Solvent system[a]						
	A	B	C	D	E	F	G
II	0.22	0.41	0.43	0.38	–	–	–
III	0.13	0.25	–	0.38	0.43	0.40	0.30
V	0.25	0.40	0.51	0.53	0.70	0.30	–
IX	0.12	0.23	0.43	0.37	0.55	0.10	–
VIII	0.20	0.50	0.48	0.35	0.21	–	–
VII	0.12	0.23	0.45	0.40	0.54	0.15	0.29
X	0.23	–	0.53	0.50	0.66	0.25	–
XI	0.16	0.30	0.49	0.42	–	0.22	–

[a] A, *n*-butanol (18)-water (83); B, ammonium citrate (pH 4.4) (18)-ethanol (82); C, *n*-butanol (4)-ethanol (1)-water (5) (upper layer); D, *iso*-propanol (4)-0.2 *N* ammonium hydroxide (1); E, saturated $NH_4H\,CO_3$ solution; F, *iso*-propanol (4)-water (1); G, *iso*-propanol (6)-water (2)-ammonia (0.880) (3).

when the less stable boat conformation is considered (Table I).

Altropyranoside (III) was synthesized by treatment of 2-amino-2-*deoxy*-D-altrose with ethyl *N*-[carbomoyl(cyano)methyl] formimidate[5] (IV) at pH 8. The product was extremely sensitive to ice-cold dilute acid, alkali, and even to warm water but it was successfully purified by chromatography on DEAE-cellulose at 4 °C using water as eluant and the eluted material could be freeze-dried without decomposition. The product appeared to be homogeneous on thin layer chromatograms (Table II), showed spectroscopic values consistent with structure (III) (Table III), and gave a purple colour in the BRAT-

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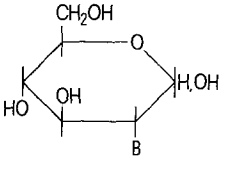

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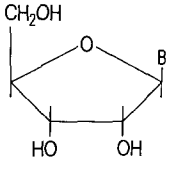

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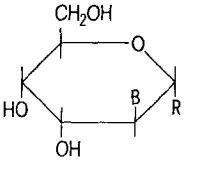
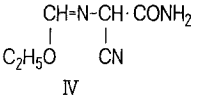


III R=OH
V R=OCH3



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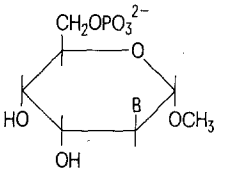

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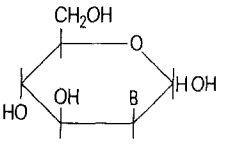

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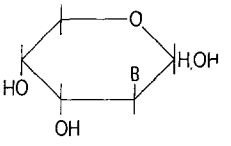
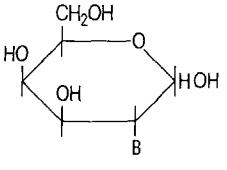


VIII



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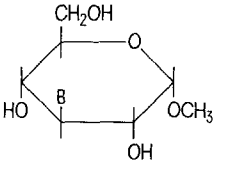
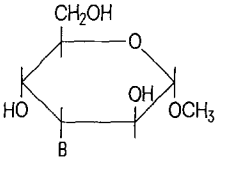


X



XI

In the formulae above B:

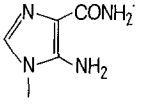


Table III. Spectroscopic and periodate titration data for nucleoside analogues

Compound	Spectrum in acid λ_{max} (nm)	ε	Spectrum in neutral solution λ_{max} (nm)	ε	Spectrum in alkali λ_{max} (nm)	ε	Spectrum in the Bratton-Marshall test λ_{max} (nm)	ε	Periodate titration mole equivalent of 10_4-consumed
II	246,267	10,200	267	10,300	265–6	10,900	540	26,000	1.01
III	246,276	8,450	266–7	10,200	265–6	10,900	545	15,100	2.98
V	242,267	9,400	265	10,500	265	10,650	552	14,800	1.02
VI	244,268	8,000	267	10,000	268	10,600	550	24,600	1.03
IX	246,267	9,600	267	10,700	267	10,650	550	13,200	2.99
VIII	246,266	9,800	265	10,000	267	10,100	545	12,900	2.05
VII	244,267	9,100	267	11,000	265	11,500	549	14,150	2.33
X	242,267	10,200	265	10,900	267	11,650	545	13.500	0
XI	245,267	11,600	267	10,400	267	11,650	550	21,050	0

Table IV. Purification of nucleoside analogues by column chromatography on ion-exchange resins

Compound	Resin type	Column dimensions	Elution with water at flow rate (ml/h)	Major fraction emerged between (ml)
III	DE 52	32 × 2.0	12	63– 85
IX (picrate) [a]	DE 52	15 × 1.0	15	70– 91
V	AG 1 × 8 (Formate) 200–400 mesh	58 × 3.5	33	116–164
VI	,,	19 × 1.5	48	246–317 [b]
VIII	,,	45 × 3.5	45	324–404
X	,,	16.5 × 3.0	33	146–252
XI	,,	32 × 3.5	33	175–294

[a] a crystalline picrate was formed by adding aqueous picric acid, this was collected, washed, dissolved in water and applied to the column; [b] washed initially with water (112 ml) then eluted with M-formic acid.

TON-MARSHALL test[6] indicative of aminoimidazoles. The compound quickly darkened in dilute acid to produce a black solid (mp > 350 °C) which did not move from the origin on t.l.c. plate and is presumably a polymer.

For in vitro studies nucleotides are often preferred to nucleosides but the acid sensitivity of compound (III) precluded phosphorylation directly. Therefore, the related methyl 2-altropyranoside derivative (V) was synthesized from methyl 2-amino-2-*deoxy*-D-altropyranoside[7] and imidate (IV). This glycoside was much more stable to acid and alkali and could be purified on an ion-exchange column (Table IV) and phosphorylated by the method of TENER[8]. Despite the fact that the 2′-and 4′-hydroxyl groups were not protected during the phosphorylation reaction the 6′-monophosphate (VI) was the only major product, after purification by ion-exchange chromatography it had a similar electrophoretic mobility to AMP and GMP, contained 1 mole equivalent of phosphate, consumed 1 mole equivalent of periodate[9], gave a purple colour in the BRATTON-MARSHALL test and showed the characteristic ultraviolet spectrum of an aminoimidazole.

A number of other 2′-substituted analogues were synthesized from the appropriate amino sugar. Both the mannose derivative (VII) and arabinose derivative (VIII) have a simliar stereochemistry to (II). The galactose compound (IX) which is related to the α-anomer[10] of (II) was also prepared. All these compounds mutarotate in water and are unstable in acid although they decompose at a slower rate than compound (III).

The method was also applied to the synthesis of 3′-(amino-imidazole carboxamide) derivatives from the methyl glycosides of 3-amino-3-*deoxy*-D-glucose and 3-amino-3-*deoxy*-D-altrose[11]; as expected, the products (X and XI) did not consume periodate but were otherwise similar to the isomeric 2′-examples (Tables II and III).

Experimental procedures. The 2-amino-2-*deoxy*-D-monosaccharide hydrochloride (270 mg) (or methyl glycoside, etc.) dissolved in a minimum volume of water was adjusted to pH 8.0 with solid potassium bicarbonate and then diluted to 8 ml with methanol. Ethyl *N*-[carbamoyl-(cyano)methyl] formimidate (350 mg) was added and the mixture kept at room temperature for 24 to 48 h. The mixture was evaporated to dryness in a rotary evaporator at 38 °C. The residue was dissolved in methanol and again evaporated then redissolved in water and purified by column chromatography (Table IV). In one case (compound VII) the product crystallized out when the reaction mixture was concentrated and chromatographic purification was unnecessary. Most of the methods used in characterising the products we have described elsewhere[4,10]. Electrophoresis was carried out on a Shandon flat bed apparatus at 10 °C using Whatman 3 mm paper at 2 volts per cm at *pH 1.85* [acetic acid (15)-formic acid (10)-water (255) (v/v)], *pH 9.4* [in NaH CO_3 (56.8) (N · Na_2CO_3 (14.4)-water (929) (v/v)], and *pH 9.1* (1% sodium tetraborate in water); products were detected using a) the BRATTON-MARSHALL spray reagents[12] and b) ammonium molybdate spray reagents for phosphate[13].

Zusammenfassung. Es wird eine Reihe von Imidazolglykosiden und deren Synthese beschrieben. Diese eignen sich als Analoga der natürlichen Nukleoside für biologische Versuche.

D. V. WILSON and C. G. BEDDOWS

Department of Pathology, University of Cambridge, Cambridge, Polytechnic of the South Bank, London S.E. 1 (Great Britain), 6 August 1973.

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Prostaglandins During Development. II. Identification of Prostaglandin 9-Hydroxy Dehydrogenase Activity in Adult Rat Kidney Homogenates

An earlier investigation of the major prostaglandin-inactivating enzymes, prostaglandin 15-hydroxy dehydrogenase (15-PGDH) and Δ-13 reductase (13-PGR), in rat lungs revealed age-related changes in the activity of these enzymes. The high 13-PGR activity observed in foetal and early postnatal vs. adult rats suggested to us that an efficient inactivation of the prostaglandins and primary metabolites might constitute an important feature of cell