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3-β-D-ERYTHROFURANOSYL-1-PHENYLPYRAZOLO[3,4-*b*]QUINOXALINE, A NEW *C*-NUCLEOSIDE ANALOG*

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ABSTRACT

Dehydration of the hydroxyalkyl chain of 1-phenyl-3-(D-*arabino*-tetritol-1-yl)pyrazolo[3,4-*b*]quinoxaline gave the *C*-nucleoside 3-β-D-erythrofuranosyl-1-phenylpyrazolo[3,4-*b*]quinoxaline (**2**) in 82% yield The structure, and the configuration at the anomeric carbon atom, of **2** were elucidated by periodate oxidation, c d and n m r spectroscopy, and mass spectrometry N m r -spectral and c d studies revealed that, due to the large size of the heterocyclic base, compound **2** is formed by inversion in the configuration of C-1 of the side chain The mechanism of the dehydrative cyclization with inversion is discussed

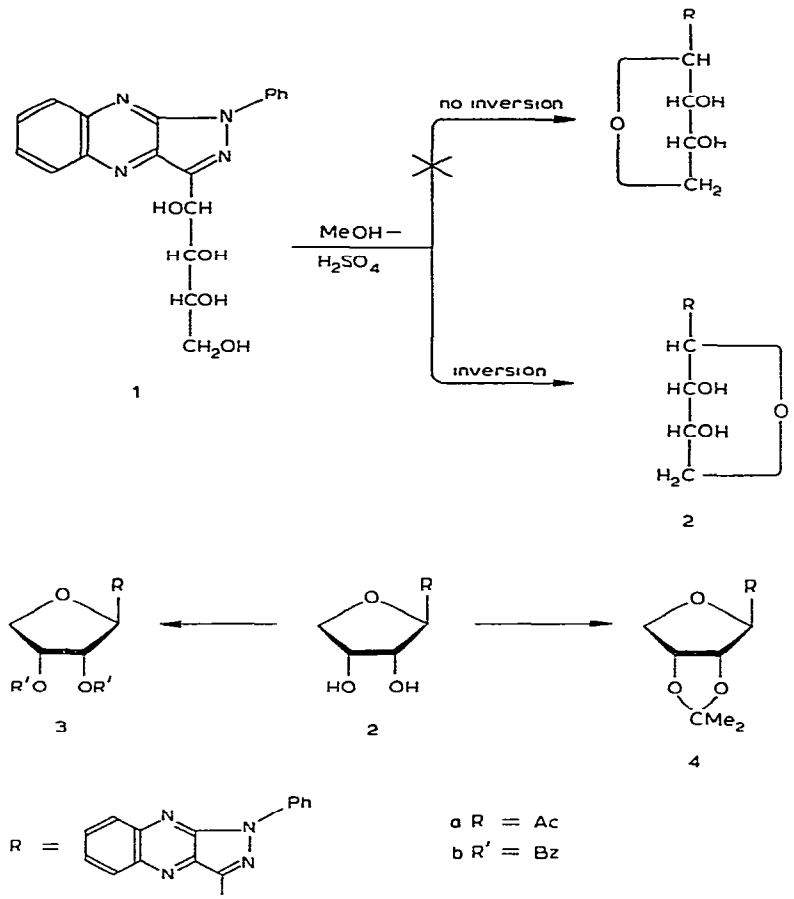
IHTRODUCTION

C-Nucleoside analogs have a glycosyl group attached to a nitrogen heterocycle at a ring-carbon atom, instead of a ring-nitrogen atom This carbon–carbon linkage is more stable than the glycosyl carbon–nitrogen bond of true nucleosides which makes the compounds useful tools for biochemical investigations and for antimitotic or antiviral research[1] A satisfactory method for their synthesis is by dehydration of the hydroxyalkyl chain of *C*-(hydroxyalkylated), nitrogen-heterocyclic derivatives by use of a strong acid 3,6-Anhydro triazoles[2 3] and anhydro benzimidazoles[4 5] were prepared by this method, but it has not been extensively used for preparing other *C*-nucleoside analogs, possibly because of uncertainty as to the anomeric configuration of the products

The present work describes the synthesis (in 82% yield) and structure of a new type of *C*-glycosylated, nitrogen heterocycle, namely, 3-β-D-erythrofuranosyl-1-phenylpyrazolo[3,4-*b*]quinoxaline (**2**), by dehydrative cyclization of 1-phenyl-3-(D-*arabino*-tetritol-1-yl)pyrazolo[3,4-*b*]quinoxaline (**1**) with methanolic sulfuric acid The anomeric configuration of **2** was established by c d and n m r spectroscopy The dehydrative cyclization of **1** was effected with inversion in the configuration of C-1′,

*This work was carried out, in part, at the Organic Chemistry Laboratories, The Norwegian Institute of Technology University of Trondheim, Trondheim-NTH Norway

to give **2**, having the D-*erythro* configuration (see Scheme 1) This type of inversion was observed during the cyclization of saccharide osazones[6] having the *trans* configuration at C-3 and C-4 in the Fischer projection formulas



Scheme 1

The structure of the *C*-nucleoside **2** was elucidated as follows (*a*) The results of elemental analysis agreed with the values calculated for a (monoanhydro-alditol-yl)phenylpyrazoloquinoxaline [(monoanhydro-alditol-yl)phenylflavazole] having the molecular formula $C_{19}H_{16}N_4O_3$ Its high-resolution mass spectrum showed *m/e* 348 121 (calc 348 122) (*b*) On periodate oxidation, it consumed one mole of oxidant per mole, in agreement with a furanose ring-structure (*c*) Acetylation of **2**, either with acetic anhydride–pyridine, or by refluxing with acetic anhydride, afforded a diacetyl derivative (**3a**) whose elemental analysis agreed with the formula $C_{23}H_{20}N_4O_5$, and whose high-resolution mass spectrum showed *m/e* 432 143 (calc 432 143) The n m r spectrum of **3a** showed two methyl signals, at δ 2 09 and

2 19, attributable to two acetyl groups (*d*) Benzoylation of **2** with benzoyl chloride–pyridine afforded a dibenzoyl derivative (**3b**), whose high-resolution mass spectrum showed *m/e* 556 172 (calc for $C_{33}H_{24}N_4O_5$, 556 175) (*e*) The u v spectra of compounds **1**, **2**, and **3** showed the absorption maxima expected for a glycosyl-phenylpyrazolo[3,4-*b*]quinoxaline[7] (*f*) The anomeric configuration (at C-1′) of the *C*-nucleoside prepared was determined by n m r -spectral studies as follows The anomeric proton of **2** appeared to overlap with one of the hydroxyl protons at δ 5 34, as a triplet of two-proton intensity After the addition of CD_3CO_2D, the signal for the hydroxyl proton disappeared, and the signal for the anomeric proton appeared, as a doublet having J 6 9 (see Fig 1) Likewise, a coupling constant of 6 7 Hz for the anomeric proton at δ 5 68 was obtained for the diacetyl derivative **3a**, and subsequent

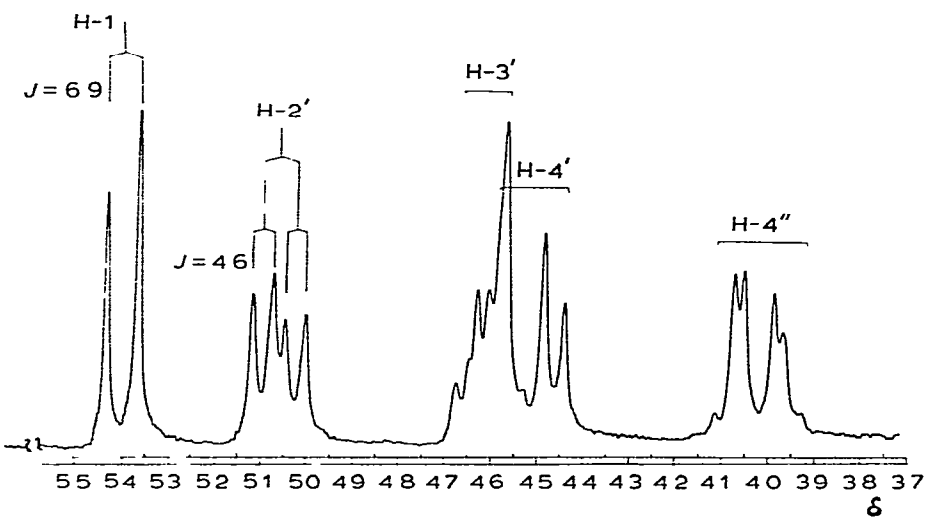


Fig 1 N m r spectrum, at 100 MHz, of 3-β-D-erythrofuranosyl-1-phenylpyrazolo[3,4-*b*]quinoxaline (**2**) + CD_3CO_2D (high resolution of the sugar moiety)

acetylation caused little or no effect on the coupling constant for the anomeric proton This large coupling-constant of the anomeric proton in **2** and **3a** made assignment of the anomeric configuration difficult Unless low enough[8 9] (less than 3 5 Hz)[10], the coupling constant of β-nucleosides cannot be ascertained Leonard and Laursen[11] stated that, if a ribofuranose ring is constrained by fusion with a second ring, the coupling constants between H-1′ and H-2′ of β-nucleosides are lowered, while those for α-nucleosides are unaffected[8] Accordingly, the isopropylidene derivative (**4**) of **2** was prepared, and its 100-MHz, n m r spectrum (see Fig 2) was recorded It showed two methyl signals of the isopropylidene group at δ 1 66 and 1 46, and, at lower field, the methylene group at C-4′, which appeared as a narrow multiplet at δ 4 16–4 19, the signal for H-3′ appeared as a multiplet at δ 5 19–5 30, and at lower field, that for H-2′, a doublet at δ 4 56 with $J_{2\ 3}$ 6 0 and $J_{1\ 2}$ 0 6 The signal for the

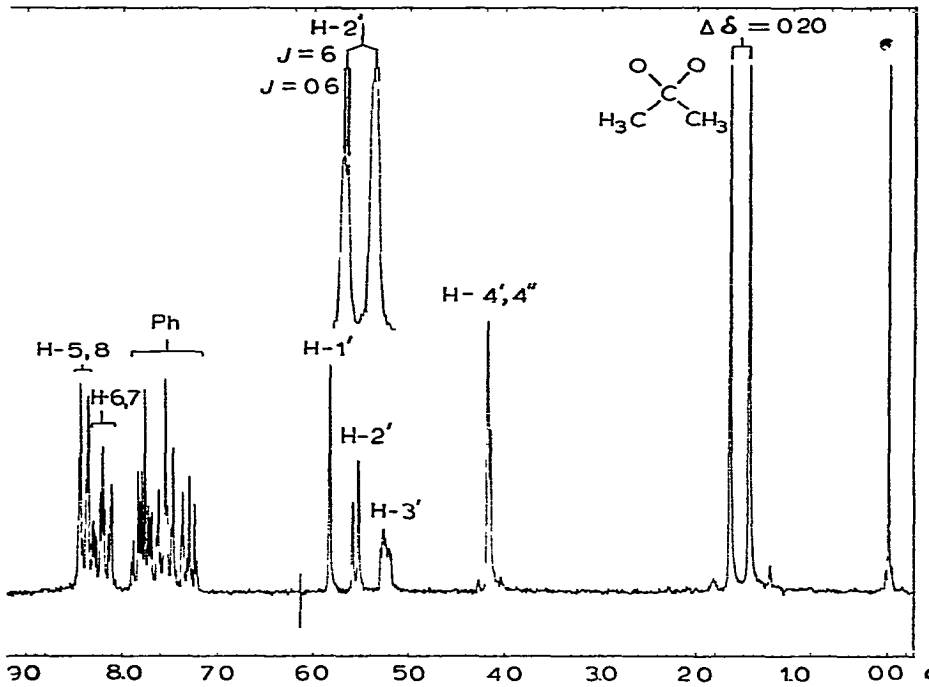


Fig 2 N m r spectrum at 100 MHz, of 3-(2,3-*O*-isopropylidene-*β*-D-erythrofuranosyl)-1-phenylpyrazolo[3,4-*b*]quinoxaline

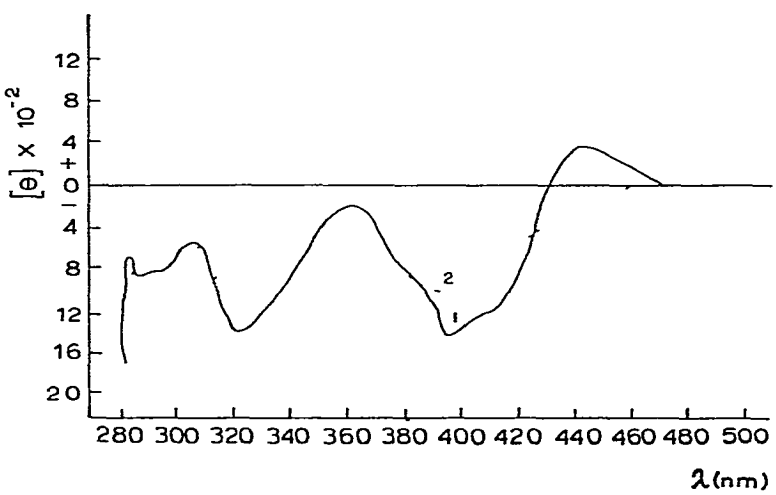


Fig 3 C d spectra of (1) 1-phenyl-3-(D-*arabino*-tetritol-1-yl)pyrazolo[3,4-*b*]quinoxaline (———), and (2) 3-*β*-D-erythrofuranosyl-1-phenylpyrazolo[3,4-*b*]quinoxaline (– – – – –)

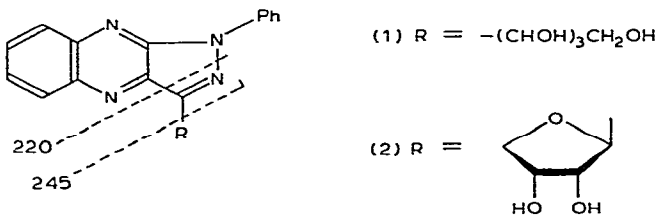
anomeric proton appeared as a singlet at δ 5 84, with $J_{1\ 2} < 1$ Hz, indicative of the β configuration

It is known[12–14] that the configuration of the anomeric carbon atom in nucleosides could be determined from the difference ($\Delta\delta$) between the chemical shift of the methyl signals of the 2,2-dimethyldioxolane ring, for β anomers, $\Delta\delta$ is $\geqslant 0\ 18$, and for α anomers, $\Delta\delta$ is $\leqslant 0\ 10$ The difference of 0 20 (1 66 – 1 46) between the chemical shifts of the two methyl protons of **4** is, therefore, consistent with the β configuration; this β configuration, revealed by the n m r studies, corresponds to an inversion in the configuration of C-1′ during the dehydrative cyclization of the hydroxyalkyl substituent in **1**

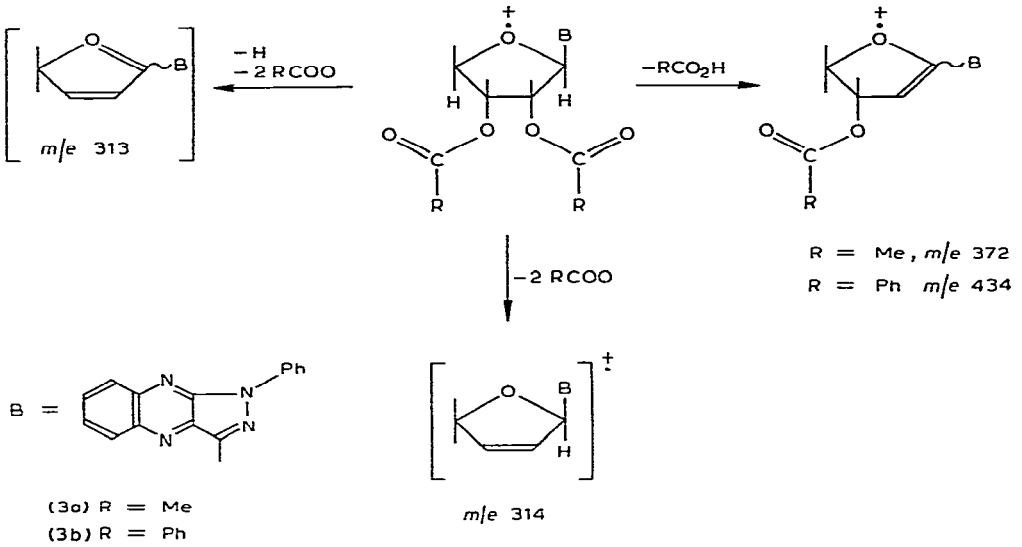
Additional evidence for this inversion in configuration was obtained from the optical properties of **2** and **1** The *C*-nucleoside **2** showed the larger, negative, specific rotation ($[\alpha]_D^{22}$ in pyridine **2**, −122 6°, **1**, −30 4°) However, in their circular dichroism (c d) spectra, they showed multiple Cotton-effect curves (see Fig 3) Compound **2** exhibited a negative maximum at 425 nm, overlapping with the adjacent, strong, negative Cotton effect, whereas **1** showed a positive maximum at 442 nm Evidently, this opposite Cotton effect at the higher wavelength absorption for **2** and **1** indicates opposite configurations of the carbon atom adjacent to the nitrogen-heterocyclic ring, and confirms occurrence of inversion in the configuration during the dehydrative cyclization of **1**

This dehydrative cyclization may be explained by a mechanism involving the formation of an unsaturated intermediate which is identical to the one suggested for the formation of 3,6-anhydro-osazones and 3,6-anhydro-osotriazoles[15] This intermediate is formed when N-1 of the 1-phenylpyrazolo[3,4-*b*]quinoxaline donates an unbonded electron to N-2, causing migration of the double bond to C-1′ of the alkyl chain and subsequent loss of OH^- Cyclization then takes place by the attack of O-4′ of the sterically favored rotamer, which has the 1-phenylpyrazolo[3,4-*b*]-quinoxaline group *trans* to the 2′-hydroxyl group The dehydration of the (hydroxy-alkyl)-1-phenylpyrazolo[3,4-*b*]quinoxalines is more stereospecific than that of the phenylosazones and osotriazoles, due to the bulkier 1-phenylpyrazolo[3,4-*b*]-quinoxaline group which consequently produces only the β anomer The other (sterically unfavored) anomer was not detected in the reaction mixture by t l c

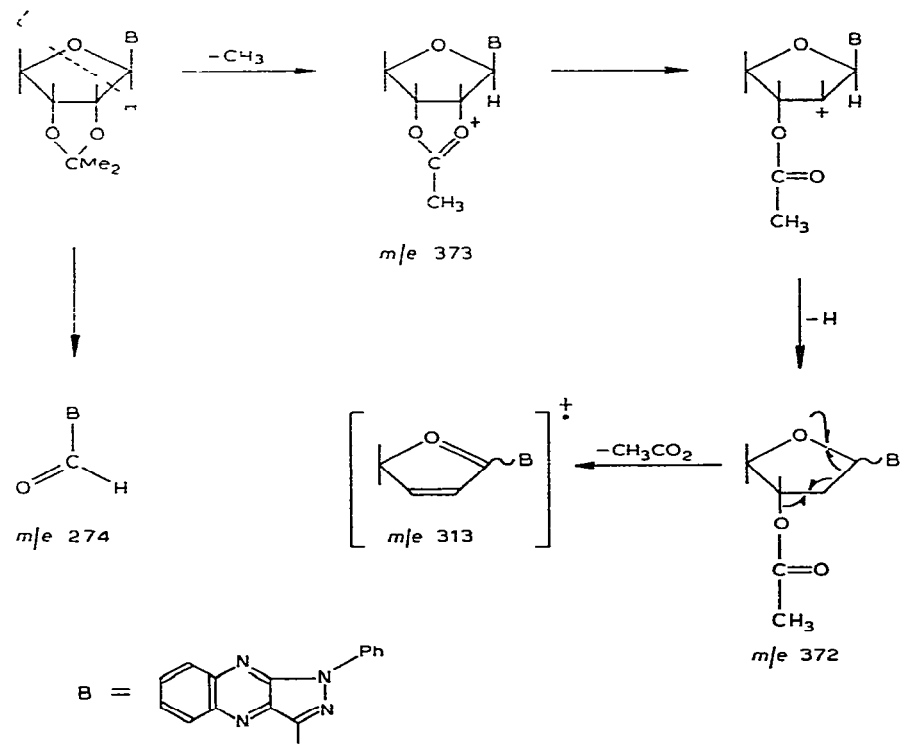
The mass spectra of **1**, **2**, **3a**, **3b**, and **4** showed the characteristic fragments of the 1-phenylflavazoles[16 17], at *m/e* 220, 245, and 247 Of these three ions, the first



Scheme 2



Scheme 3



Scheme 4

two arise as illustrated in Scheme 2, whereas *m/e* 247 represents BH_2, which is due to α-cleavage and double hydrogen-transfer to the base moiety The ionic species B–CH=$\overset{+}{O}$H, found at *m/e* 275 (B+30, B = 1-phenylflavazole residue), represents the base peak for **1** and **2**, but is less intense for **3a**, **3b**, and **4** The fragmentation pattern of **3a**, **3b**, and **4** to give the peak at *m/e* 313 is shown in Schemes 3 and 4, respectively This peak represents the base peak for **3a**, but is less intense for **3b** and **4** The abundance of the fragment *m/e* 313 for **3a**, **3b**, and **4** may be considered to be additional evidence for the furanose ring-structure The base peak at *m/e* 105 for **3b** represents the PhCO group, and, for **4**, the base peak at *m/e* 274 represents the BCHO fragment

From these results, it was concluded that compound **2** is 3-β-D-erythro-furanosyl-1-phenylpyrazolo[3,4-*b*]quinoxaline

EXPERIMENTAL

General — Melting points are uncorrected Evaporations were performed under diminished pressure below 50° Thin-layer chromatography (t l c) was conducted on silica gel (Kiesel gel G, Merck) with butanone saturated with water as the solvent, and the yellow spots were detected under ultraviolet light (bright fluorescence) U v absorption spectra were recorded, for solutions in 1,4-dioxane, with a Cary 17 instrument Circular dichroism measurements were recorded with a Cary 60 spectropolarimeter, for solutions in 1,4-dioxane, at a dynode voltage not >0 75 kV N m r spectra were recorded with Varian A-60 A (^{1}H, 60 MHz), Perkin–Elmer R-32 (90 MHz) Varian FT (80 MHz), and Varian XL (100 MHz) instruments Mass spectra were obtained with AEI Ms 902 and DUPONT MS 21-492 spectrometers Combustion analyses were performed in the Department of Chemistry, Purdue University

1-Phenyl-3-(D-arabino-*tetritol-1-yl*)*pyrazolo*[*3,4-*b*]*quinoxaline* (**1**) — A solution of D-*glycero*-D-*gulo*-heptose[18] (6 8 g) in water (250 mL) was heated with *o*-phenylenediamine (3 g), phenylhydrazine hydrochloride (19 g), and glacial acetic acid (7 mL) in a sealed flask for 6 h in a boiling-water bath The flask was cooled, and opened, and the yellow precipitate was filtered off, washed successively with water, 50% methanol, and ether, and dried, yield 6 g Recrystallization from propyl alcohol gave yellow needles, m p 231–233°, $[\alpha]_D^{22}$ −30 4° (*c* 2 3 pyridine), $\lambda_{max}^{1,4\text{-dioxane}}$ 269, 334, and 410 nm (log ε 4 7, 4 1, and 3 7) ν_{max}^{KBr} 3350 (OH) and 1605 cm^{-1} (C=N), n m r data (90 MHz, Me_2SO-d_6–CD_3CO_2D) δ 3 45–3 82 (m, 2 H, H-4′,4″), 3 83–4 07 (m, 1 H, H-3′), 4 35 (q, 1 H, H-2′, $J_{1,2}$ 3 1 Hz, $J_{2,3}$ 8 Hz) 5 73 (d, 1 H, H-1′), 7 33–8 16 (m, 5 H, Ph), 8 30–8 46 (m, 2 H, H-6,7), and 8 6–8 74 (m, 2 H, H-5,8), mass-spectral data *m/e* 367 (2, M + 1), 366 (8, M), 332 (5), 301 (10), 297 (8), 277 (10*), 276 (60*, BH–CH=$\overset{+}{O}$–H), 275 (100, B–CH=$\overset{+}{O}$H, where B = 1-phenylflavazole moiety), 274 (24, B–CH=O), 260 (7) 257 (7), 247 (21, BH_2), 246 (12, BH), 245 (29, B), 220 (14, BH_2–HCN), 77 (19, Ph), 56 (22), 44 (20), 43 (10), and 40 (18), accurate

measurement of the molecular-ion peak Found 366 1329 (Calc 366 1328), circular dichroism data in 1,4-dioxane (*c* 0 5 mg/mL) at 22° 470 ([*θ*] 0), 442 (+351), 430 (0), 410 [−1215 (sh)], 396 (−1427), 380 [−732 (sh)], 362 (−205), 321 (−1420), 305 (−549), 293 [−820 (sh)], 286 (−878), 284 (−695), and 283 (−1830)

Anal Calc for $C_{19}H_{18}N_4O_4$ C, 62 3, H, 5 0, N, 15 3 Found C, 62 5, H, 4 9, N, 15 2

*3-β-*D*-Erythrofuranosyl-1-phenylpyrazolo[3,4-*b*]quinoxaline* (**2**) — A suspension of **1** (1 g) in 6% methanolic sulfuric acid solution (500 mL) was boiled under reflux, with stirring, for 60 h, complete dissolution occurred in ~4 h The reaction was monitored by t l c , complete dehydration was found after 60 h (only one spot) The solution was poured into hot water, and the methanol was evaporated on a hot-water bath in a current of hot air The yellow precipitate obtained was collected, washed thoroughly with water until neutral, and dried, yield 0 78 g (82%) It was recrystallized from methanol, to give yellow needles, m p 225–227°, $[\alpha]_D^{22}$ −122 6° (*c* 2 1, pyridine, $\lambda_{max}^{1,4\text{-dioxane}}$ 268, 334, and 410 nm (log ε 4 7, 4 1, and 3 8), ν_{max}^{KBr} 3390 (OH) and 1605 cm^{-1} (C=N), n m r data (90 MHz, Me_2SO-d_6) δ 3 97 (q, 1 H, H-4″), 4 33–4 7 (m, 2 H, H-4′,3′), 5 02 (d of d, 1 H, H-2′), 5 19 (d, 1 H, OH), 5 26–5 45 (t, 2 H, H-1′ and OH), and 7 32–8 46 (m, 9 H, aromatic protons), after addition of CD_3CO_2D, the two hydroxyl protons disappeared (n m r , 100-MHz data) δ 5 34 (d, H-1′, $J_{1,2}$ 6 9), 5 1 (dd, H-2′, $J_{2,3}$ 4 6), 4 52 (m, H-3′, $J_{3,4}$ 4 1, $J_{3,5}$ 2 7), 4 44 (H-4′, $J_{4,5}$ 9), and 3 93 (H-4″) (the chemical shifts of H-3′, H-4′, and H-4″ were determined by Internuclear Double Resonance (INDOR) and their coupling constants by use of the LAOCN3 Computer program) mass-spectral data *m/e* 349 (10, M + 1), 348 (46, M), 301 (5), 289 (22), 276 (22, BH–CH=$\overset{+}{O}$–H), 275 (100*, B–CH=$\overset{+}{O}$H), 274* (4, B–CHO), 259 (8, B–CH_2), 247 (8, BH_2), 246 (5, BH) 245 (16, B), 220 (12, BH_2–HCN). 102 (5), 77 (21, Ph), and 51 (8), accurate measurement of the molecular-ion peak Found 348 1214 (Calc 348 1222), circular dichroism data in 1,4-dioxane (*c* 0 53 mg/mL) at 22° 463 ([*θ*] 0), 396 (−886), 352 (−197), 334 (−722), 330 (−394), 324 (−755), 320 (−447), 316 [−591 (sh)], 311 (−886), 293 (−250), and 283 (−1510)

Anal Calc for $C_{19}H_{16}N_4O_3$· C, 65 49 H, 4 63, N, 16 10 Found C, 65 24, H, 4 76. N, 16 00

Periodate oxidation of **2** — A suspension of **2** (22 76 mg) in water (2 mL) was treated with 0 2M sodium metaperiodate for 24 h at room temperature in the dark, with occasional magnetic stirring After dilution to 100 mL, it was treated with an excess of sodium arsenite, and back-titrated against iodine solution Periodate consumption 1 01 mol (based on M 348) In a control experiment, using methyl α-D-mannopyranoside under the same conditions, 1 9 mol of periodate was consumed (based on M 194)

*3-(2,3-Di-*O*-acetyl-β-*D*-erythrofuranosyl)-1-phenylpyrazolo[3,4-*b*]quinoxaline* (**3a**) — A solution of **2** (0 1 g) in pyridine (2 mL) was treated with acetic anhydride (2 mL) for 24 h at room temperature, it was then poured onto crushed ice, and the acetate was filtered off, washed with water, and dried, yield 0 15 g It was recrystal-

lized from methanol, to give yellow needles, m p 145–146°, $[\alpha]_D^{22}$ −104 3° (*c* 2 25, chloroform), λ_{max}^{MeOH} 267, 334, and 408 nm (log ε 4 7, 4 1, and 3 7), ν_{max}^{KBr} 1750 (OAc) and 1605 cm^{-1} (C=N), n m r data (80 MHz, $CDCl_3$) δ 2 08 and 2 19 (d, 6 H, 2 CH_3CO), 4 67 and 4 21 (2 q, 2 H, ABX system of the methylene group at C-4′, $J_{3\ 4'}$ 3 4 and $J_{3\ 4}$ 4 8, respectively, with a geminal $J_{4\ 4}$ 10 3 Hz), 5 68 (d, 1 H, H-1′, $J_{1\ ,2}$ 6 7), 5 81–5 97 (m, 1 H, H-3′), 6 24 (q, 1 H, H-2′, $J_{2\ 3}$ 5 2 Hz), and 725–8 51 (m, 9 H, aromatic protons), mass-spectral data *m/e* 432 (8, M), 373 (3, M−Ac), 372 (13, M−AcOH), 314 (26, M−2 OAc), 313 (100, M−H−2 OAc), 301 (7), 287 (5, M−H−2 OAc–CN), 276 (4, BH–CH=$\overset{+}{O}$H), 275 (16, B–CH=$\overset{+}{O}$H), 274 (3, BCHO), 247 (2, BH_2), 246 (3, BH), 245 (9, B), 220 (5, BH_2–HCN), 115 (22), 77 (13, Ph), and 43 (64, CH_3CO), accurate measurement of the molecular-ion peak Found 432 1431 (Calc 432 1434)

Anal Calc for $C_{23}H_{20}N_4O_5$ C, 63 87, H, 4 66, N, 12 96 Found C, 63 98, H, 4 69, N, 12 83

Refluxing of **2** *with acetic anhydride* — Compound **2** (20 mg) was refluxed with acetic anhydride (5 mL) for 5 h, the solution poured onto crushed ice, and filtered, and the solid washed, and dried Recrystallized from methanol it gave yellow needles, m p and mixed m p with **3a**, 144–145°

*3-(2,3-Di-*O*-benzoyl-β-*D*-erythrofuranosyl)-1-phenylpyrazolo[3,4-*b*]quinoxaline* (**3b**) — A solution of **2** (0 2 g) in pyridine (3 mL) was treated with benzoyl chloride (0 13 mL) for 3 days at room temperature, poured onto crushed ice, the suspension filtered, and the solid washed with water, and dried, yield 0 3 g It was recrystallized from methanol, to give yellow needles, m p 154–155°, ν_{max}^{KBr} 1735 (OBz) and 1605 cm^{-1} (C=N), mass-spectral data *m/e* 556 (1, M), 434 (12, M−$PhCO_2H$), 314 (17, MH−2 PhCOO), 313 (75, M−2 PhCOO) 312 (7, M−H−2 PhCOO), 286 (6), 275 (14, B–CH=$\overset{+}{O}$–H), 247 (2, BH_2), 246 (4, BH), 245 (9, B), 220 (4, BH_2–HCN), 177 (17), 122 (7, $PhCO_2H$), 106 (9), 105 (100, PhCO), 97 (7), 95 (7), 94 (7), 91 (6, PhN), 85 (7), 84 (7), 83 (11), 82 (5) 81 (6), 79 (5), 78 (7, PhH), 77 (64, Ph), 76 (5), 73 (9), 71 (7), 70 (7), 69 (23), 68 (5), 67 (8), 65 (5), 58 (10), 57 (43), 56 (18), and 55 (31), accurate measurement of the molecular-ion peak Found 556 172 (Calc 556 175)

*3-(2,3-*O*-Isopropylidene-β-*D*-erythrofuranosyl)-1-phenylpyrazolo[3,4-*b*]quinoxaline* — A solution of **2** (65 mg) in acetone (10 mL) was treated with *p*-toluenesulfonic acid[19] (320 mg), with stirring After 2 h, t l c showed the reaction to be complete (one spot, R_F 0 84) The mixture was poured into an ice-cold solution of sodium hydrogencarbonate, and the resulting precipitate was filtered off, washed with water, and dried, yield 84 mg (90%) It was recrystallized from methanol, to give yellow needles, m p 160–161° λ_{max}^{MeOH} 268, 336, and 408 nm (log ε 4 5, 4 0, and 3 5), ν_{max}^{KBr} 1600 (C=N) and 1390 cm^{-1} (CMe_2), n m r data (100 MHz, $CDCl_3$) δ 1 46 and 1 66 (d 6 H, CMe_2, Δδ 0 20), 4 16–4 19 (2 H, H-4′,4″), 5 19–5 30 (m, 1 H, H-3′), 5 56 (q, 1 H, H-2′, $J_{2',3}$ 6 0 Hz, $J_{1\ ,2}$ 0 6 Hz), 5 84 (s, 1 H, H-1′), 7 23–7 84 (m, 5 H, Ph), 8 06–8 16 (m, 2 H, H-6,7), and 8 17–823 (m, 2 H, H-5,8) mass-spectral data *m/e* 390 (2, M+2), 389 (12, M+1), 388 (39, M), 373 (9, M−CH_3), 372 (5, M−CH_3−H),

331 (6), 330 (17, M−CH_3COCH_3), 329 (40, M−CH_3−C(=$\overset{+}{O}$–H)–CH_3), 315 (7), 313 (13, M−CH_3−AcOH), 302 (17), 301 (60), 300 (5), 299 (5), 289 (11), 287 (37), 286 (7), 285 (10), 284 (5), 276 (13, BH–CH=$\overset{+}{O}$–H), 275 (68, B–CH=$\overset{+}{O}$–H), 274 (100, B–CHO), 273 (25, B–C≡$\overset{+}{O}$), 272 (12), 271 (7), 260 (9), 259 (9), 247 (BH_2), 246 (10, BH), 245 (79, B), 244 (8, B–H), 220 (10, BH_2–HCN), 219 (13, BH–HCN), 218 (10, B–HCN), 187 (14), 158 (5), 157 (18), 145 (8), 143 (7), 129 (5), 116 (5), 115 (5), 103 (7), 102 (10), 101 (10), 92 (5), 91 (11), 90 (10), 85 (5), 78 (5, PhH), 77 (50, Ph), 76 (8), 65 (6), 64 (8), 63 (5), 59 (13, CH_3–C(=$\overset{+}{O}$–H)–CH_3), 58 (67, CH_3COCH_3), 57 (6), 51 (18), and 43 (33. CH_3–$\overset{+}{C}$O), accurate measurement of the molecular-ion peak Found, 388 154 (Calc 388 154)

Anal Calc for $C_{22}H_{20}N_4O_3$ C, 68 01, H, 5 16, N, 14 43 Found C, 68 25, H, 5 17, N, 14 44

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