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Synthesis and ^{1}H NMR studies of 3-(D-*erythro*-glycerol-1-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline and its 7-chloro and 7-methyl analogues

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Abstract

3-(D-*erythro*-Glycerol-1-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline and its 7-chloro and 7-methyl analogues (**11** and **12**) were prepared from the corresponding quinoxalines. The 7-substituted analogues **11** and **12** were obtained as the preponderant isomers, and the 6-substituted analogues as the minor isomers. The structure and position of the substituent were determined by ^{1}H NMR studies. The effect of substitution on the chemical shift of other protons is discussed.

Keywords: Quinoxaline; Pyrazolo[3,4-*b*]quinoxaline; 7-Chloro and 7-methyl analogues

1. Introduction

Pyrazolo[3,4-*b*]quinoxalines are compounds of biological interest [1–3]. The 1-aryl analogues are yellow compounds whose insolubility militates against the extensive study of their biological activity [4]. Substitution at the base moiety of 1-aryl analogues [5–8] did not improve the solubility of these compounds. The 1-aryl analogues are prepared by condensation of the sugar, *o*-phenylenediamine, and the corresponding arylhydrazine, in a one-pot reaction, or by first preparing the quinoxaline intermediate, from the sugar and *o*-phenylenediamine, then condensing it with the corresponding arylhydrazine. 3-(D-*erythro*-Glycerol-1-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline (**9**) and its 7-chloro, and 7-methyl analogues (**11** and **12**) were prepared. The structure, position of the substituent on the base moiety and its effect on the chemical shift of other protons were determined by ^{1}H NMR studies.

2. Results and discussion

Condensation of D-glucose, *o*-phenylenediamine (**1**), and hydrazine hydrate in the usual manner in a one-pot reaction did not give the expected 3-(D-*erythro*-glycerol-1-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline (**9**) directly, as the reaction stopped at the stage of the quinoxaline intermediate **4** (Scheme 1). However, treatment of **4** with hydrazine hydrate gave **9** in 45% yield. Compound **9** is formed through the 1′-hydrazone intermediate [4]. Although the

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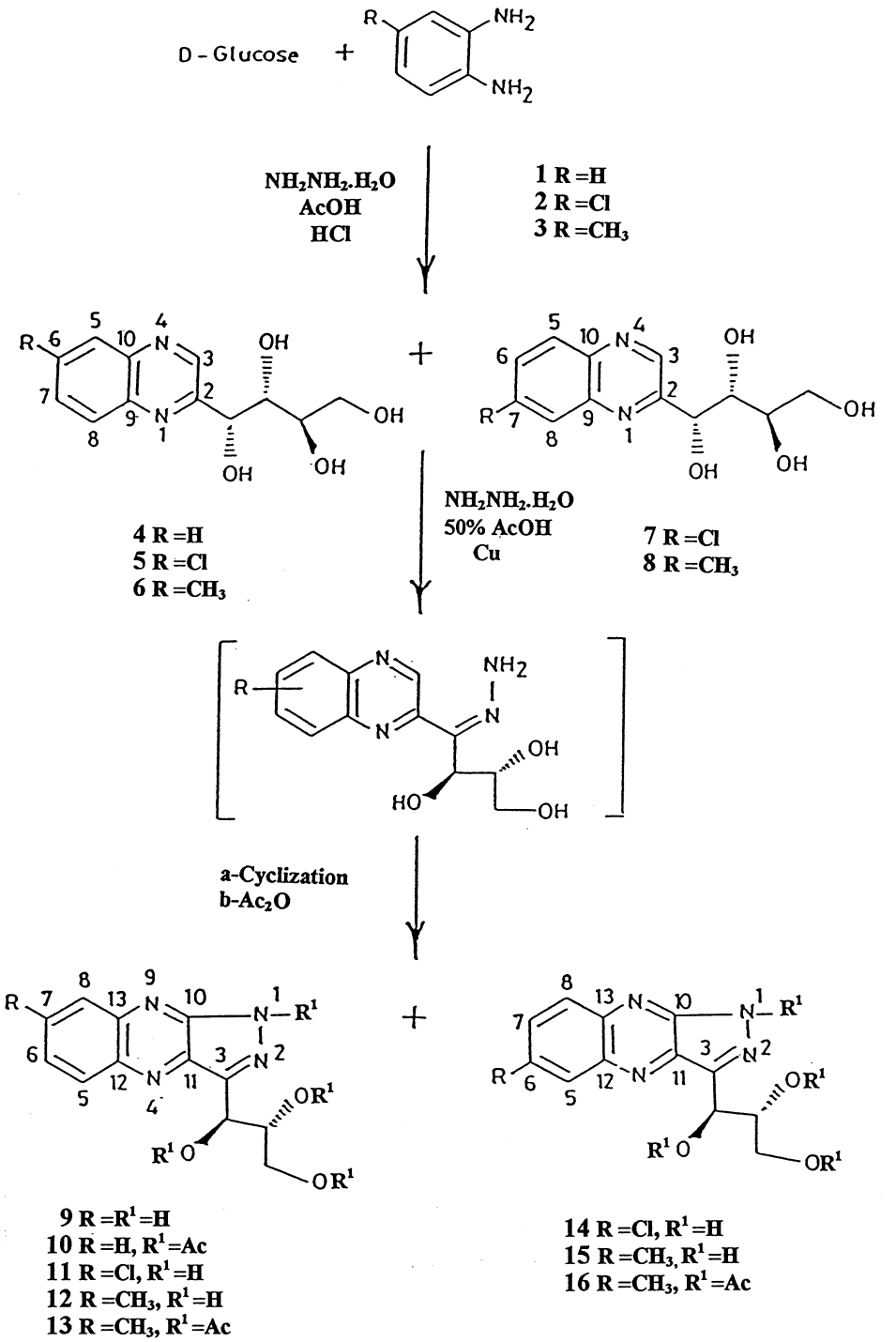
yield of **9** is slightly lower than that of the corresponding 1-aryl analogues [5–8], it showed better solubility.

The coupling constant values of the polyhydroxyalkyl side-chain protons for **9**, $J_{1',2'}$ 8.8 Hz and $J_{2',3'}$ 2.5 Hz, are in accord with a dominant contribution to the conformational equilibrium by the extended planar–zigzag (***P***) conformation [9,10]. These coupling constant values are close to the values obtained for the sugar protons of the 1-aryl analogues [9], indicating that replacement of the 1-aryl group by a 1-hydrogen atom in compound **9** did not affect the population of the planar–zigzag conformation of the polyhydroxyalkyl side chain.



Scheme 1.

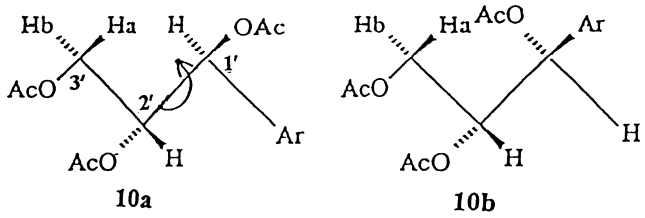


Fig. 1. Planar–zigzag conformation of the polyacetoxyalkyl side chain.

Acetylation of **9** gave the *N*-acetyl-tetra-*O*-acetyl derivative **10**. In the ^{1}H NMR spectrum, the coupling constant $J_{1',2'}$ 5.9 Hz is lower than that for compound **9** ($J_{1',2'}$ 8.8 Hz). This indicates that compound **10** has a substantial population of the rotamer having these protons gauche disposed, which is obtained by rotation around the C-1′–C-2′ bond (see Fig. 1).

A comparison of the ^{1}H NMR spectra of compounds **9** and **10** (Table 1) indicates that, as expected, the sugar proton signals of **10** are shifted downfield due to α-acetylation, and this downfield shift decreases from H-1′ to H-3′ as we go further from the base moiety. At the base moiety, acetylation of the polyhydroxyalkyl chain causes a smaller downfield shift of the aromatic protons. The H-5 proton was the most downfield-shifted, owing to its proximity to the anisotropic effect of the polyacetoxyalkyl chain. This induction effect acting through space resulted in a reversal of the chemical shift order of H-5 and H-8 of compound **9** as shown from their observed coupling constant values. For **9**, H-8 is the most downfield signal; however, for **10**, H-5 is the most downfield signal. Although the spectra of compounds **9** and **10** were carried out in two different solvents (Me_2SO-d_6 for **9**, and $CDCl_3$ for **10**) and the effect of different solvents on the chemical shift cannot be neglected, the solvent should have a parallel effect on all protons. It is however likely that the change of solvent may cause the difference in population of conformers that is observed for **9** and **10**.

In order to define the chemical shift order of the aromatic protons of compound **9**, the synthesis of 7-monosubstituted analogues was explored as an alternative to the deuterium labelling synthon usually required for this assignment. The 7-chloro (**11**) and 7-methyl (**12**) analogues having substituents with opposite inductive effects at position 7 were prepared

Table 1
^{1}H chemical shifts (δ) and first-order coupling constants (J, Hz) for compounds **9**–**12** at 400 MHz

Compound	H-1′	H-2′	H-3′a	H-3′b	H-5	H-6	H-7	H-8	NH	OH(OAc)
9 [a]	4.98d $J_{1'2'}$ 8.8	4.43m	3.84dd $J_{2'3'a}$ 2.5 $J_{3'a3'b}$ 11.2	3.64dd $J_{2',3'b}$ 5.9	8.13d $J_{5,6}$ 8.8	7.92dd $J_{6.7}$ 7	7.82dd	8.28d $J_{7,8}$ 8.3	13.66s	5.63s, 1′-OH 4.43m, 2′-OH, 3′-OH
10 [b]	6.63d $J_{1'2'}$ 5.9	6.01 m	4.58dd $J_{2'3'a}$ 3.4 $J_{3'a3'b}$ 12.2	4.44dd $J_{2'3'b}$ 6.4	8.36d $J_{5,6}$ 8.8	7.94m	7.87m	8.30d $J_{7,8}$ 8.3		(2.1s) (2.04s) (2.24s) (2.92s, N–Ac)
$\Delta\delta_{9,10}$ [c]	−1.65	−1.58	−0.74	−0.80	−0.23	−0.02	−0.05	−0.02		
11 [a]	4.99d $J_{1'2'}$ 8.3	4.53m	3.84dd $J_{2'3'a}$ 2.9 $J_{3'a,3'b}$ 11.2	3.66dd $J_{2',3'b}$ 5.9	8.16d $J_{5,6}$ 9.3	7.92dd		8.35d $J_{6,8}$ 2.4	13.88bs	5.65s, 1′OH 4.50d, 2′-OH 4.48t, 3′-OH
$\Delta\delta_{9,11}$ [c]	−0.01	−0.10	0.00	−0.02	−0.03	0.00		−0.07	−0.22	
12[a,b,d]	4.98q $J_{1'2'}$ 8.3	4.41m	3.83m	3.64dd $J_{2'3'b}$ 5.9 $J_{3'a,3'b}$ 11.2	8.02d $J_{5,6}$ 9.3	7.74dd		8.03d $J_{6,8}$ 1.5	13.67s	5.58d, 1′-OH 4.50d, 2′-OH 4.48, 3′-OH
$\Delta\delta_{9,12}$ [c]	0.00	+0.02	+0.01	0.00	+0.11	+0.18		+0.25	−0.01	

[a] In Me_2SO-d_6.
[b] In $CDCl_3$.
[c] Positive $\Delta\delta$ value means upfield shift; negative $\Delta\delta$ value means downfield shift.
[d] Aromatic CH_3 was observed at δ 2.59.

and their ^{1}H NMR spectra were studied in comparison with the spectrum of compound **9**.

Condensation of D-glucose, 4-chloro-*o*-phenylenediamine (**2**) and hydrazine hydrate in acidic medium in a one-pot reaction gave an isomeric mixture of 6-chloro-2-(D-*arabino*-tetritol-1-yl)quinoxaline (**5**) and 7-chloro-2-(D-*arabino*-tetritol-1-yl)quinoxaline (**7**) (Scheme 1) with the predominance of the 6-chloro analogue **5** [11]. The two isomers **5** and **7** showed the same R_f value on TLC; however, the ^{1}H NMR spectrum of the mixture showed, downfield, the H-3 signal, characteristic of quinoxalines, as two close singlets at δ 9.15 and 9.14 in the ratio of 5:4 as calculated from their ^{1}H NMR integrals (lit. [11] ratio 87:13 in favour of the 6-chloro isomer).

Refluxing this quinoxaline mixture **5** and **7** with hydrazine hydrate in acidic medium gave the corresponding 7(6)-chloro-3-(D-*erythro*-glycerol-1-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline (**11** and **14**) with the predominance of the 7-chloro isomer **11**. The major 6-chloroquinoxaline isomer **5** gives the major 7-chloro-1*H*-pyrazolo[3,4-*b*]quinoxaline analogue (**11**), which has the same position of the substituent, but with different numbering.

The ^{1}H NMR spectrum of **11** and **14** showed in the aromatic region the presence of two isomers corresponding to the major 7-chloro isomer **11** and the minor 6-chloro isomer **14** (see Fig. 2(b)). Fractional recrystallization of the mixture of **11** and **14** three times from methanol resulted in the separation of the pure major isomer **11**.

Similarly, refluxing D-glucose, 4-methyl-*o*-phenylenediamine (**3**) and hydrazine hydrate in acidic medium, in a one-pot reaction, afforded the 6- and 7-methyl-2-(D-*arabino*-tetritol-1-yl)quinoxaline mixture (**6** and **8**), with the predominance of the 6-methyl isomer **6**. Isolation and subsequent condensation of the mixture of **6** and **8** with hydrazine hydrate in acidic medium gave the corresponding 3-(D-*erythro*-glycerol-1-yl)-7(6)-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline mixture (**12** and **15**), with the predominance of the 7-methyl isomer **12**. The ^{1}H NMR spectrum of **12** and **15** showed in the aromatic region an isomeric constitution of the 7- and 6-methyl analogues **12** and **15** in the ratio of 10:1 (see Fig. 2(c)). The major isomer **12** was separated in spectrally pure form by fractional recrystallization of the mixture of **12** and **15** from methanol.

The position of the substituent in the preponderant isomers **11** and **12** was assigned by comparing the ^{1}H NMR spectra (aromatic region) of **11** and **14** (Fig. 2(b)) and **12** and **15** (Fig. 2(c)) with that of the unsubstituted analogue **9** (Fig. 2(a)). The triplet corresponding to H-7 of compound **9** was absent due to substitution by a chlorine atom or a methyl group at this position, and the multiplicity of the signal corresponding to H-6 was reduced by the adjacent 7-substituent. In addition, the most downfield doublet at δ 8.28 ($J_{7,8}$ 8.3 Hz) corresponding to H-8 for compound **9** was observed as a narrow doublet at δ 8.35 having a small meta-coupling constant ($J_{6,8}$ 2.4 Hz) for the 7-chloro isomer **11**, with a small downfield shift ($\Delta\delta_{9,11}$ −0.07), and as a singlet at δ 8.03 for the 7-methyl isomer **12** with an upfield shift ($\Delta\delta_{9,12}$ +0.25). The signal corresponding to H-5 was shown as a doublet having a large coupling constant ($J_{5,6}$ 9.3 Hz) for both compounds **11** and **12** due to the ortho coupling of H-5 with the adjacent H-6 proton. These observations were reflected for the minor isomers **14** and **15** having substituents at position 6. The low-intensity upfield signal corresponding to H-7 for **14** (Fig. 2(b)) was observed as a quartet at δ 7.82 ($J_{7,8}$ 8.8 Hz), and for **15** (Fig. 2(c)) as an apparent triplet at δ 7.65 ($J_{7,8}$ 8.3 Hz) due to the large ortho coupling of H-7 with H-8. The corresponding low-intensity H-5 signal was shown as a narrow doublet for the minor isomer **14** at δ 8.21 having a small meta-coupling constant ($J_{5,7}$ 2.4 Hz) with a small downfield shift due to the adjacent chlorine atom, and as a singlet for the minor isomer **15** at δ 7.88 with a little upfield shift due to the adjacent methyl group. The H-8 signal was shown as a low intensity doublet at δ 8.30 for **14** and δ 8.14 for **15** having a large coupling constant; $J_{7,8}$ 9.3 and 8.8 Hz, respectively. These results are in accord with substitution at position 7 for the major isomers **11** and **12**, and position 6 for the minor isomers **14** and **15**. The ^{1}H NMR spectral pattern for the mixture **11** and **14**, as well as for **12** and **15**, in the sugar region did not manifest an isomeric constitu-

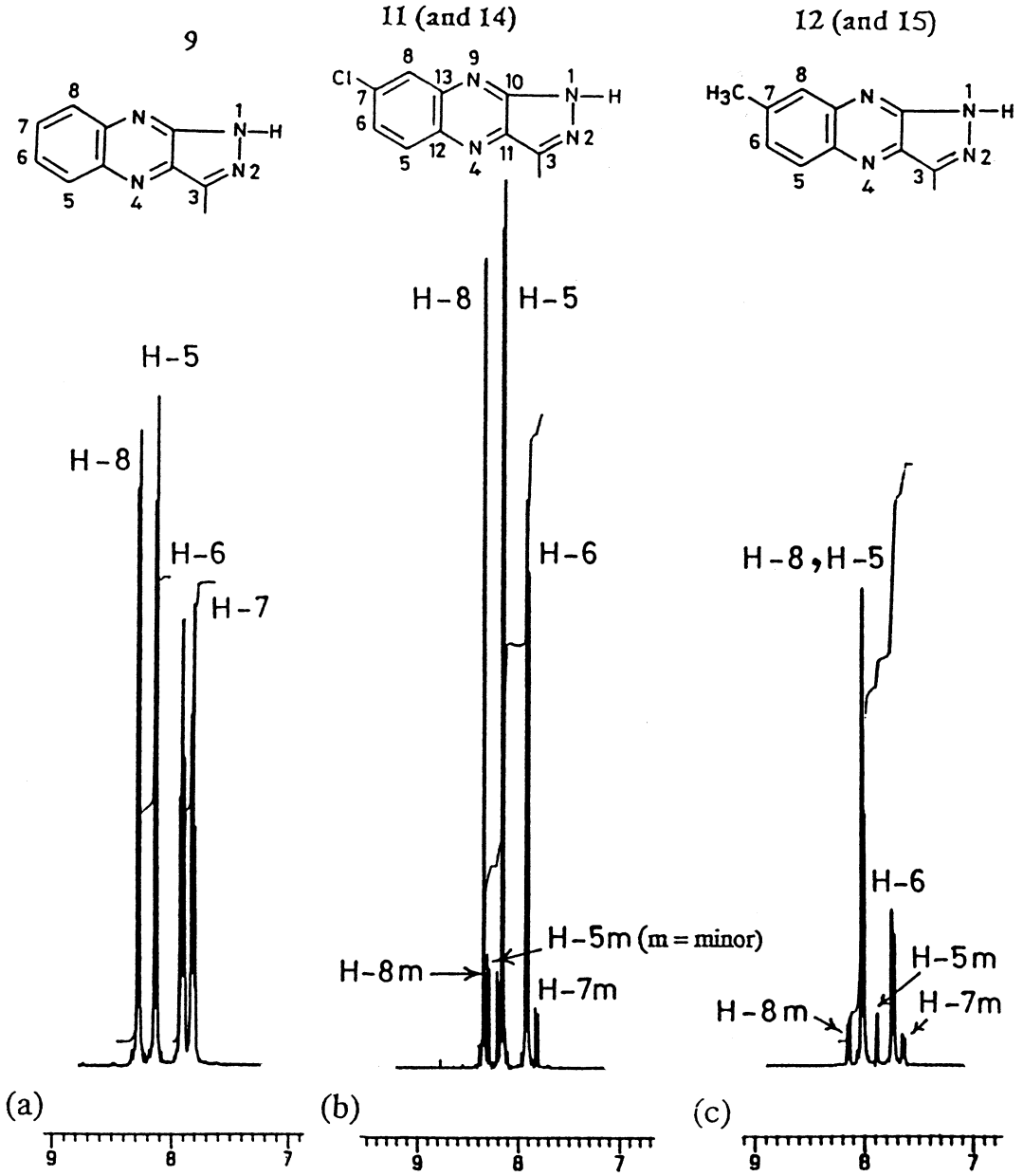


Fig. 2. ^{1}H NMR spectra at 400 MHz, in Me_2SO-d_6, for the base moiety of (a) 3-(D-*erythro*-glycerol-1-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline (**9**); (b) 7(6)-chloro-3-(D-*erythro*-glycerol-1-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline (**11** and **14**); and (c) 3-(D-*erythro*-glycerol-1-yl)-7- and -(6)-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (**12** and **15**).

tion in contrast to the spectra in the aromatic region.

*Assignment of the aromatic protons of the 1*H*-pyrazolo[3,4-*b*]quinoxaline base moiety.*— From these comparative ^{1}H NMR spectral studies for compounds **9** and **11** on the one hand and **9** and **12** on the other, the assignment of the aromatic protons H-5, H-6, H-7 and H-8 for the unsubstituted analogue **9** (Fig. 2(a)) can be confirmed. Since the most downfield doublet for compound **9** collapsed for the major isomers **11** and **12**, into a narrow doublet for **11** or a singlet for **12** due to substitution at this position, the most downfield doublet at δ 8.28 for **9** can be assigned to H-8, and the next upfield doublet at δ 8.13 to H-5, which is opposite to the assignment used before [5]. Similarly, since substitution at position 7 for compounds **11** and **12** resulted in the disappearance of the upfield triplet of compound **9**, this upfield triplet at δ 7.82 for **9** can be assigned to H-7,

and the next downfield triplet at δ 7.92 to H-6. In conclusion, the aromatic protons of compound **9**, and for polyhydroxyalkyl-1*H*-pyrazolo[3,4-*b*]quinoxalines in general, are in the following downfield order δ H-8 > H-5 > H-6 > H-7. This conclusion can alternatively be reached only by deuterium labelling techniques.

Inductive effect of the substituent at position 7 on the chemical shift of other protons.—A comparison of the chemical shift values for compounds **9** and **11** and **9** and **12** (Table 1) indicates that substitution at position 7 by the electron-attractive chlorine atom resulted in a small downfield shift for the aromatic protons. However, substitution by the electron-releasing methyl group resulted in an upfield shift. The effect of the methyl group is large and that of the chlorine atom is small. Substitution at the base moiety did not change the population of the planar–zigzag conformation of the polyhydroxyalkyl side chain as shown from the coupling values of the sugar protons. Similar behaviour was noticed for the 1-aryl-1*H*-pyrazolo[3,4-*b*]quinoxaline analogues [9].

Acetylation of **12** and **15** gave the *N*-acetyl-tri-*O*-acetyl derivatives (**13** and **16**). The ^{1}H NMR spectrum showed in the aromatic region the same phenomenon of exchanging the chemical shift order of H-5 and H-8. This exchange seems to be a general feature for the pyrazolo[3,4-*b*]quinoxaline base moiety as a result of acetylation of the polyhydroxyalkyl chain.

3. Conclusions

From these comparative ^{1}H NMR spectral studies of pyrazolo[3,4-*b*]quinoxaline analogues, it can be concluded that:

1. (a) The synthesis of monosubstituted analogues from 4-substituted-*o*-phenylenediamines affords two isomers with the predominance of the 7-substituted isomer. (b) Substitution at the base moiety does not change the population of the planar–zigzag conformation of the polyhydroxyalkyl side chain. A small downfield shift for the sugar protons is observed and H-1′ is the most affected one. (c) In the aromatic region, the electron-attracting chlorine atom exerts a small downfield shift on the aromatic protons and the electron-releasing methyl group shows an upfield shift. The effect of the methyl group is large, and the effect of chlorine is small.

2. Acetylation of the polyhydroxyalkyl chain resulted in: (a) A planar–zigzag conformation of the polyacetoxyalkyl chain, with some contribution of the rotamer having a gauche relationship of H-1′ and H-2′. (b) A downfield shift of the sugar protons due to α-acetylation, the effect decreasing as we go away from the base moiety; H-1′ > H-2′ > H-3′. (c) A smaller downfield shift of the aromatic protons; H-5, which is closer to the polyacetoxyalkyl chain, showed the largest downfield shift resulting in exchanging the chemical shift order of H-5 and H-8, rendering H-5 more downfield than H-8.

3. These comparative studies can be used to predict the ^{1}H NMR spectral pattern of newly prepared polyhydroxyalkyl 1*H*-pyrazolo[3,4-*b*]quinoxaline analogues.

4. Experimental

Melting points were determined with a Fisher–Johns apparatus and are uncorrected; evaporations were performed under diminished pressure below 60 °C.

TLC was conducted on silica gel (Kieselgel G, Merck) with solvent *A*, 3:1 benzene–EtOH; solvent *B*, 3:1 EtOAc–hexane; and solvent *C*, 10:1 $CHCl_3$–MeOH. Compounds were detected under short-wavelength UV light at 254 nm. IR spectra were recorded with a Perkin–Elmer 1430 instrument. UV spectra were recorded with Perkin–Elmer Lambda 48 instrument. ^{1}H NMR spectra were recorded with Varian EM-390, Jeol EX 400, and Bruker AM 500 spectrometers at 90, 400, and 500 MHz, respectively, using Me_4Si as an internal standard. ^{13}C NMR spectra were recorded with a Bruker 500 instrument at 125.7 MHz. Mass spectra were recorded with an AEI MS 902 spectrometer. Combustion analyses were performed in the Department of Chemistry, Alexandria University, Alexandria, Egypt.

*3-(*D-erythro-*Glycerol-1-yl)-1*H-*pyrazolo-[3,4-*b*]quinoxaline* (**9**).—A mixture of 2-(D-*arabino*-tetritol-1-yl)quinoxaline [12] (**4**; 9.0 g, 36 mmol), hydrazine hydrate (11.7 mL), 50% HOAc (67.5 mL), and a few pieces of copper metal was treated as described by Buu-Hoi et al. [1]; yield 4.2 g (44.9%). The product was recrystallized from hot water, then from MeOH, to give **9** as pale-yellow needles: mp 228–230 °C (lit. [1] mp 228–229 °C); TLC (solvent *A*) R_f 0.3; λ_{max}^{EtOH} 230, 330, and 377 nm (log ε 4.0, 3.9, and 3.8); ν_{max}^{KBr}: 3364 (OH), 3144 (NH), and 1587 cm^{-1} (C=N); for ^1H NMR data see Table 1; mass spectral data (selected ions): *m/z* 260 (1, M), 229 (3, M − CH_2OH), 212 (3, BCH_2CHO; where B = 1*H*-pyrazolo[3,4-*b*]quinoxaline moiety), 211 (2, BCH_2CO), 201 (8, BH_2CHOH), 200 (73, BCH_2OH), 199 (100, BCHOH), 198 (11, BCHO), 197 (4, BCO), 184 (4, BCH_3), 183 (7, BCH_2), 172 (18, BH_3), 171 (22, BH_2), 170 (7, BH), 169 (1, B), 156 (5, BH − CH_2), 155 (3, B − CH_2), 146 (3), 145 (17), 144 (30, BH − CN), 143 (31, B − CN), 142 (3, B − HCN), 130 (3, BH − CN_2), 129 (6, B − CN_2), 119 (3), 118 (15), 117 (12), 116 (10), 115 (4), 103 (4), 102 (18), 92 (5), 91 (7), 90 (25), 89 (5), 77 (5, Ph), 76 (7), 75 (6), 65 (3), 64 (5) and 63 (5).

1-(N-*Acetyl*)-*3-(1,2,3-tri*-O-*acetyl*-D-erythro-*glycerol-1-yl)-1*H-*pyrazolo[3,4-*b*]quinoxaline* (**10**).—A suspension of **9** (1.6 g, 6 mmol) in Ac_2O (20 mL) was boiled under reflux for 3 h. The hot solution was poured onto crushed ice, and the acetate **10** was filtered off, washed successively with water, and dried; yield 2.2 g (84%). It was recrystallized from diethyl ether–light petroleum, to give colourless needles: mp 98–99 °C (lit. [13] mp 99–100 °C); TLC (solvent *B*) R_f 0.53; ν_{max}^{KBr}: 1740 (OAc); and 1573 cm^{-1} (C=N); for ^1H NMR data see Table 1; mass spectral data (selected ions): *m/z* 428 (0.3, M), 387 (2, MH_2 − Ac), 386 (10, M − CH_2=CO), 368 (3, M − AcOH), 344 (12), 327 (8), 326 (39, M − OAc − Ac), 309 (2, M − AcOH − OAc), 285 (9, BH_2CHOAc; where B = 1-(*N*-Acetyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline moiety), 284 (52, BHCHOAc), 283 (5, BCHOAc), 267 (5), 243 (6, $BHCH_2OH$), 242 (37, BCH_2OH), 241 (16, BCHOH), 226 (4, BCH_3), 225 (21, BCH_2), 224 (14, BCH), 213 (6, BH_2), 212 (4, BH), 211 (3, B), 201 (7), 200 (51, M − B − OH), 199 (65, M − BH − OH), 197 (6, BH − CH_3), 196 (3, B − CH_3), 184 (2, B − HCN), 172 (2, BH − CN_2), 171 (6, B − CN_2), 170 (4), 145 (6), 144 (6), 143 (6), 103 (6), 102 (4), 90 (3), 60 (7, CH_3COOH), 45 (8) and 43 (100, CH_3CO).

*6- and 7-Chloro-2-(*D-arabino-*tetritol-1-yl)quinoxaline* (**5** *and* **7**).—A solution of D-glucose (4.5 g, 25 mmol) in water (100 mL) was heated with **2** (3.6 g, 25 mmol), hydrazine hydrate (8.2 mL), concd HCl (7 mL), and glacial HOAc (7 mL) in a sealed flask for 4 h in a boiling-water bath. The flask was cooled, opened, and the precipitate obtained was filtered off, washed successively with water, 50% EtOH, and ether, then dried; yield 6.0 g (85%). It was recrystallized from MeOH, to give colourless needles [11]: mp 184–186 °C; TLC showed one spot, R_f 0.35 (solvent *A*) and 0.24 (solvent *C*); ^1H NMR data (400 MHz; Me_2SO-d_6): δ 3.49 (m, 2 H, H-4′a, H-4′b), 3.70 (m, 2 H, H-2′, H-3′), 4.42 (m, 1 H, 4′-OH), 4.62 (d, 1 H, 3′-OH, $J_{3',OH}$ 6.8 Hz), 4.76 (d, 1 H, 2′-OH, $J_{2',OH}$ 3.9 Hz), 5.18 (d, 1 H, H-1′, $J_{1',2'}$ 5.9 Hz), 5.70 (q, 1 H, 1′-OH, *J* 2.4, 5.9 Hz), 7.85 [m, 1 H, H-6(7)], 8.11 (m, 1 H, H-8), 8.18 (d, 1 H, H-5, $J_{5,7}$ 2 Hz), 9.14 [s, 1 H, H-3(minor)], and 9.15 (s, 1 H, H-3); after addition of CD_3CO_2D, the four hydroxyl protons disappeared: δ 3.49 (m, 2 H, H-4′a, H-4′b), 3.68 (m, 2 H, H-2′, H-3′), and 5.18 (s, 1 H, H-1′). Anal. Calcd for $C_{12}H_{13}ClN_2O_4$: C, 50.63; H, 4.60; N, 9.84. Found: C, 50.19; H, 4.85; N, 9.72.

*7- and 6-Chloro-3-(*D-erythro-*glycerol-1-yl)1*H-*pyrazolo[3,4-*b*]quinoxaline* (**11** *and* **14**).—A mixture of **5** and **7** (3 g, 10 mmol), hydrazine hydrate (3.4 mL), 50% HOAc (20 mL), and a few pieces of copper metal was boiled under reflux for 6 h. The solution was cooled and the precipitate obtained was filtered off, washed successively with water, and dried; yield 1.3 g (42%). It was recrystallized from hot water, then from MeOH, to give pale-yellow needles: mp 246–248 °C; TLC showed one spot, R_f 0.33 (solvent *A*) and 0.23 (solvent *C*); for ^1H NMR data see Table 1; the minor isomer **14** showed the following low-intensity peaks in the aromatic region: δ 7.82 (q, 1 H, H-7, $J_{5,7}$ 2.4, $J_{7,8}$ 8.8 Hz), 8.21

(nd, 1 H, H-5, $J_{5,7}$ 2.4 Hz), and 8.30 (d, 1 H, H-8, $J_{7,8}$ 9.3 Hz); ^{13}C NMR data (125.7 MHz; Me_2SO-d_6): low-intensity peaks in the aromatic region only: δ 126.8 (C-5), 128.3 (C-8), 131.8 (C-7), 135.1, 135.7, 138.7 (C-10, C-11, C-6), 141.1, 144.1 (C-12, C-13) and 147.7 (C-3). Anal. Calcd for $C_{12}H_{11}ClN_4O_3$: C, 48.91; H, 3.76; N, 19.01. Found: C, 48.64; H, 3.79; N, 19.15.

*7-Chloro-3-(*D-erythro-*glycerol-1-yl)-1*H-*pyrazolo[3,4-*b*]quinoxaline* (**11**).—Fractional recrystallization of the crude mixture of **11** and **14** three times from MeOH gave the major isomer **11** as pale-yellow needles: mp 247–249 °C; R_f 0.36 (solvent *A*); the ^{1}H NMR spectrum showed the same chemical shift values as Table 1. In the aromatic region the small peaks corresponding to the minor isomer **14** were absent. ^{13}C NMR data (125.7 MHz; Me_2SO-d_6): δ 63.4 (C-3′), 68.3 (C-1′), 73.0 (C-2′), 128.3 (C-5), 130.3 (C-8), 131.3 (C-6), 131.8, 135.8, 139.5 (C-10, C-11, C-7), 140.1, 144.0 (C-12, C-13) and 147.4 (C-3).

*6- and 7-Methyl-2-(*D-arabino-*tetritol-1-yl)quinoxaline* (**6** *and* **8**).—A solution of D-glucose (3.6 g, 20 mmol) in water (80 mL) was heated with **3** (2.4 g, 20 mmol), hydrazine hydrate (6.6 mL), concd HCl (5 mL), and glacial HOAc (5 mL) in a sealed flask for 4 h in a boiling-water bath. The flask was cooled, opened, and the precipitate obtained was filtered off, washed successively with water, 50% EtOH and ether, then dried; yield 2.6 g (52%). It was recrystallized from MeOH, to give pale-yellow needles: mp 176–178 °C (lit. [14] mp 177–178 °C); TLC showed one spot, R_f 0.3 (solvent *A*) and 0.22 (solvent *C*); ^{1}H NMR data (90 MHz; Me_2SO-d_6): δ 2.57 (s, 3 H, ar-CH_3), 3.57 (m, 4 H, H-2′, H-3′, H-4′a, H-4′b), 4.27 (m, 1 H, 4′-OH), 4.55 (m, 2 H, 2′-OH, 3′-OH), 5.07 (d, 1 H, H-1′, $J_{1',2'}$ 6 Hz), 5.43 (d, 1 H, 1′-OH, $J_{1',OH}$ 4.5 Hz), 7.68 (m, 3 H, H-5, H-7, H-8), and 8.93 (s, 1 H, H-3); after addition of CD_3CO_2D, the four hydroxyl protons disappeared: δ 3.57 (m, 4 H, H-2′, H-3′, H-4′a, H-4′b) and 5.07 (s, 1 H, H-1′).

*3-(*D-erythro-*Glycerol-1-yl)-7- and 6-methyl-1*H-*pyrazolo[3,4-*b*]quinoxaline* (**12** *and* **15**).—A mixture of **6** and **8** (1.1 g, 4 mmol), hydrazine hydrate (1.9 mL), 50% HOAc (10.9 mL), and a few pieces of copper metal was boiled under reflux for 6 h. The solution was cooled, the precipitate obtained was filtered off, washed successively with water and dried; yield 0.5 g (44%). It was recrystallized from MeOH, to give pale-yellow needles: mp 257–259 °C; TLC showed one spot, R_f 0.31 (solvent *A*) and 0.25 (solvent *C*); for ^{1}H NMR data see Table 1. The minor isomer **15** showed the following low-intensity peaks in the aromatic region: δ 7.65 (d, 1 H, H-7, $J_{7,8}$ 8.3 Hz), 7.89 (s, 1 H, H-5), and 8.14 (d, 1 H, H-8, $J_{7,8}$ 8.8 Hz); ^{13}C NMR data (125.7 MHz; Me_2SO-d_6): low-intensity peaks in the aromatic region only: δ 126.7 (C-5), 129.5 (C-8), 130.2 (C-7), 134.6, 138.7, 141.0 (C-10, C-11, C-6), 141.2, 144.2 (C-12, C-13) and 147.3 (C-3). Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.15; N, 20.43. Found: C, 56.28; H, 5.11; N, 20.77.

*3-(*D-erythro-*Glycerol-1-yl)-7-methyl-1*H-*pyrazolo[3,4-*b*]quinoxaline* (**12**).—Fractional recrystallization of the crude mixture of **12** and **15** three times from MeOH gave **12** as pale-yellow needles: mp 257–259 °C; R_f 0.33 (solvent *A*); the ^{1}H NMR spectrum showed the same chemical shift values of Table 1. In the aromatic region the small peaks corresponding to the minor isomer **15** were absent. ^{13}C NMR data (125.7 MHz; Me_2SO-d_6): δ 21.2 (CH_3), 63.4 (C-3′), 68.3 (C-1′), 73.0 (C-2′), 127.9 (C-5), 128.2 (C-8), 133.2 (C-6), 135.0, 137.5, 139.4 (C-10, C-11, C-7), 140.2, 143.9 (C-12,C-13) and 147.1 (C-3).

*1-(*N-*Acetyl)-3-(1,2,3-tri-*O-*acetyl-*D-erythro-*glycerol-1-yl)-7- and -6-methyl-1*H-*pyrazolo[3,4-*b*]quinoxaline* (**13** *and* **16**).—A suspension of **12** and **15** (0.2 g, 0.7 mmol) in Ac_2O (3 mL) was boiled under reflux for 3 h. The hot solution was poured onto crushed ice, and the acetate was filtered off, washed successively with water and dried; yield 0.18 g (62%). It was recrystallized from diethyl ether–light petroleum, to give yellow needles: mp 144–146 °C; TLC (solvent *B*) showed one spot, R_f 0.55; ^{1}H NMR data (400 MHz; $CDCl_3$): δ 2.00 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 2.24 (s, 3 H, OAc), 2.65 (s, 3 H, ar-CH_3), 2.91 (s, 3 H, NAc), 4.43 (q, 1 H, H-3′b, $J_{2',3'b}$ 5.9, $J_{3'a,3'b}$ 12.2 Hz), 4.58 (dd, 1 H, H-3′a,

$J_{2',3'a}$ 3.4 Hz), 6.02 (m, 1 H, H-2′), 6.63 (d, 1 H, H-1′, $J_{1',2'}$ 5.9 Hz), 7.77 (q, 1 H, H-6, $J_{5,6}$ 8.8, $J_{6,8}$ 2 Hz), 8.05 (s, 1 H, H-8), and 8.23 (d, 1 H, H-5, $J_{5,6}$ 8.8 Hz). Anal. Calcd for $C_{21}H_{22}N_4O_7$: C, 57.01; H, 5.01; N, 12.66. Found: C, 56.82; H, 5.07; N, 12.76.

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