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Mode of formation of quinoxaline *versus* 2[1*H*]-quinoxalinone rings from dehydro-D-erythorbic acid

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ABSTRACT

The mode of formation of the quinoxaline versus 2[1*H*]-quinoxalinone rings by the reaction of *o*-diamines with dehydro-D-erythorbic acid has been investigated. The study was carried out by using one and two molar equivalents of 1,2-diamino-4,5-dimethylbenzene (**3b**) to give 6,7-dimethyl-3-(1-oxo-D-*erythro*-2,3,4-trihydroxbutyl)-2[1*H*]-quinoxalinone (**4b**) and 2-(2-amino-4,5-dimethylphenylcarbamoyl)-3-(D-*erythro*-glycerol-1-yl)-6,7-dimethylquinoxaline (**6**), respectively. The former product exists predominantly as the two furanosyl anomers. Sequential reaction of **4a** with **3b** has been studied, and the location of each diamine in the product was deduced by using ^{1}H-n.m.r. spectroscopy. A mechanism for the reaction is proposed. Acetate and acetal derivatives of the compound are prepared.

INTRODUCTION

The phenomenon of fluorescence[1] has been observed for the products from the reaction of dehydro-L-ascorbic acid and its D-*erythro* analogue (**2**) with a molar equivalent of 1,2-diaminobenzene[1–11], a property that has been used for their detection and determination[1]. The structure of the products resulting from the condensation of **2** with both one and two molecules of **3a** has been recently reinvestigated[5]. The mechanism of the reaction is not clear. Whether the nucleophilic attack of the second molecule of the diamine **4a** takes place on the carbonylamido group or on the hemiacetalic carbon atom has not been established. The former pathway for a similar reaction of dehydro L-ascorbic acid[12] has been reported by investigating the reaction polarographically[7,13]. In the present work the possible products from the reaction of dehydro-D-erythorbic acid (**2**) with **3b** were first prepared. Then, a sequential reaction of **2** with **3a** and **3b**, respectively, has been studied, whereby some light was shed on the mechanism of the reaction and a preferable attack on the hemiacetalic carbon atom of **4** was deduced. The location of each diamine moiety in the reaction product could be assigned by chemical and spectral methods.

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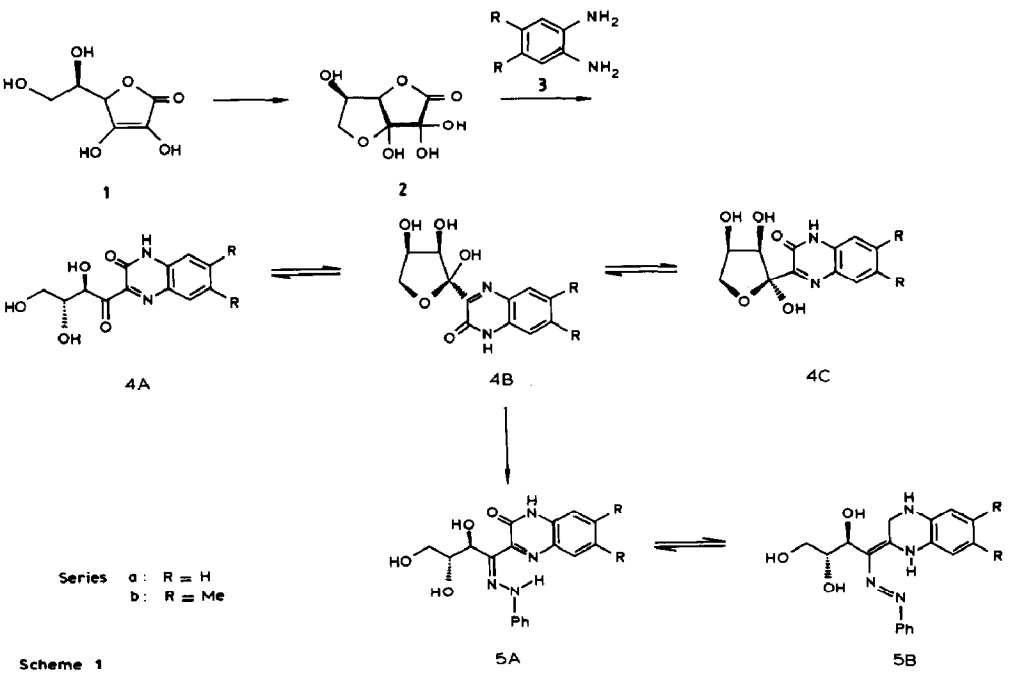
RESULTS AND DISCUSSION

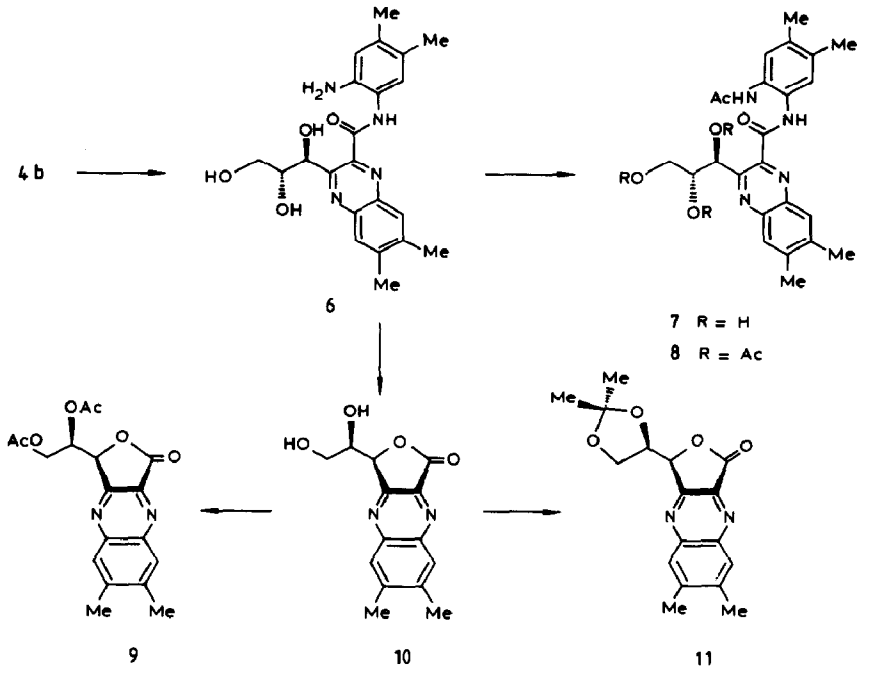
The oxidation of **1** with *p*-benzoquinone afforded dehydro-D-erythorbic acid[12], whose reaction with a molar equivalent of **3b** gave a product which was found to be an equilibrium mixture of **4A** ⇌ **4B** ⇌ **4C**. Its ^{1}H-n.m.r. spectrum showed the presence of two doublets [δ 4.76 (J 5.1 Hz) and 4.92 (J 5.7 Hz)] due to H-2 showing two closely related isomers, and each aromatic proton appeared as two singlets [(δ 7.09 and 7.12) and (δ 7.56 and 7.60)]. When the spectrum was measured at 50°, the latter pairs became two singlets and the two doublets of H-2 became sharper. It also showed a signal due to the NH which is in agreement with the structure **4**. Its ^{13}C-n.m.r. spectrum[14] showed two resonances in the anomeric region (δ 101.6 and 105.0). The latter resonance was close to the value[12] of C-3 (δ 104.8) of **2**. Consequently, it could be assigned to that of the anomer **4C**, indicating that the lactone ring was opened during the condensation. Otherwise the hemiacetal ring would have been retained, showing the presence of only one anomer. The extent of opening the furanoid ring may depend upon the substituent at C-2, as π-electron delocalization into the region may serve to facilitate furanoid ring opening[15].

The reaction of **4b** with phenylhydrazine afforded **5b** as what may be a mixture of *syn–anti* isomers similar to that proposed[6] for the methyl analogue of **1**. Alternatively, there may be a tautomeric equilibria between the hydrazone **5A** and the azo **5B**[16].

The reaction of one and two molar equivalents of **3b** with **4b** and **2**, respectively, afforded **6** whose selective acetylation gave **7** and peracetylation gave **8**. The infrared (i.r.) spectra of **6, 7,** and **8** showed the presence of one (OCN), two (2 OCN) and three (2



Scheme 1



Scheme 2

OCN and OAc) bands, respectively, in the carbonyl frequency region. Downfield shifts of the glycerolyl protons, H-1 (δ 5.13–7.10), H-2 (δ 3.80–5.70), H-3 (δ 3.55–4.54) and H-3′ (δ 3.54–4.30) were observed on acetylation of **6** to give **8**. The spectrum of **6** showed signals for the NH_2 (δ 4.61) and NH (δ 9.73), whereas that of the acetate **8** showed signals for two NH (δ 8.00 and 9.73).

Acid hydrolysis of **6** gave **10**, whose ^{1}H-n.m.r. spectrum showed H-1 as a doublet (δ 5.88) at a downfield position compared with the respective proton of its precursor **6**. This, as well as the observed downfield shifts induced on the signals of the glycerolyl moiety upon acetylation of **10** to give **9**, confirmed the size of the lactone ring. Thus, downfield shifts of H-2 (δ 4.29–5.75), H-3 (δ 3.8–4.54), and H-3′ (δ 3.80–4.40) were observed, whereas H-1 (δ 5.84) was relatively unaffected.

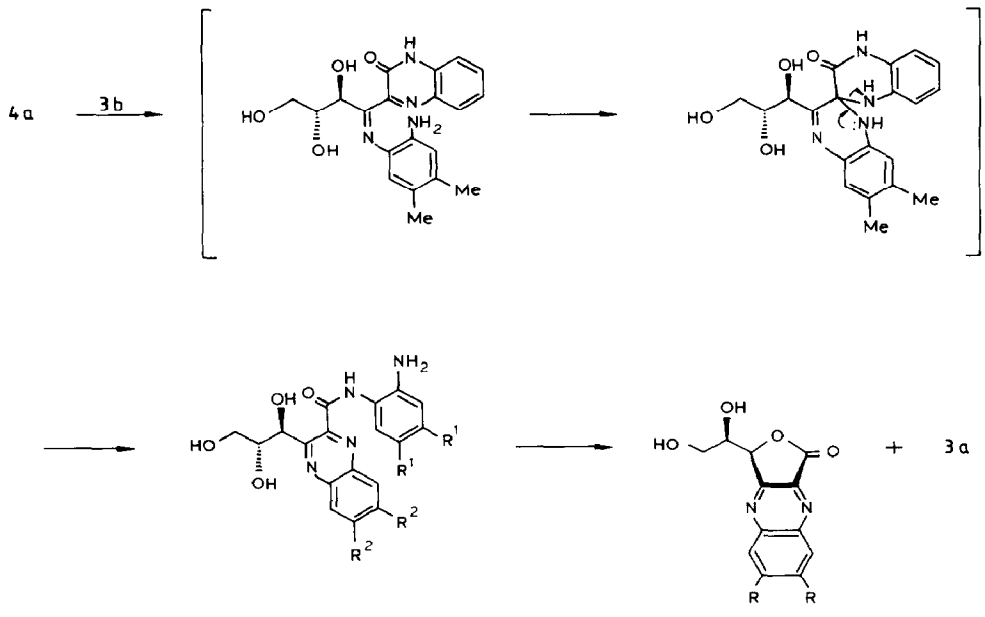
The isopropylidenation of **10** gave **11**, whose ^{1}H-n.m.r. spectrum showed the two methyl groups of the acetal ring at δ 1.07 and 1.30. The difference in their chemical shifts ($\Delta\delta$) was higher than the value anticipated from the shift rule of El Ashry[17] for an α-terminal ring and located within the range required for an *α-erythro* ring. This may be due to the greater influence of the quinoxaline ring on one of the methyl groups.

The comparison of the ^{1}H-n.m.r. spectra of the above compounds led to the conclusion that two features could be used for the characterisation of the identity of **3b** moiety, whether it is a part of a quinoxaline ring or an anilide residue. Thus, the spectrum of **10** showed a signal at δ 2.58 (2 Me). Consequently, the resonance at δ 2.12 in the spectrum of **6** could be assigned to those of the anilide residue. The second feature concerned the signals of the aromatic protons. The two aromatic protons of **10**

appeared (δ 8.04 and 8.08) at a lower magnetic field than those (δ 6.46 and 7.00) of the anilide part of **6**.

The reaction of **3b** with **4a** gave **13** and not **12**. Its structure was based on its chemical and spectroscopic characteristics. Thus, its acid hydrolysis and its reaction with acetone in presence of sulfuric acid afforded **10** and **11**, respectively, indicating that the diamine residue hydrolyzed off was **3a**. Consequently, this was the moiety that existed as the anilide part as in **13**. Otherwise, the product of hydrolysis would have been the lactone **14**. Moreover, the ^{1}H-n.m.r. spectrum of **13** showed the two methyl groups at δ 2.48, as well as the two protons of the aromatic ring carrying the two methyl groups at δ 7.90 and 7.93.

In conclusion, the reaction of the second molecule of the diamine with **4a** is most probably taking place through the nucleophilic attack of the amino group on the anomeric carbon atom rather than *via* attack on the carbonylamido group. This reaction may be followed by the attack of the second amino group on the C = N of the quinoxalinone ring to give a *spiro* intermediate whose rearrangement gives **13**. Alternatively, the first step may be the attack of the amino group on the C = N of **4a**. A similar mechanism could be proposed for the reaction of dehydro-L-ascorbic acid with *o*-diamines. However, the corresponding reaction with the derivatives[7] of dehydro-L-ascorbic acid may follow another mechanism because of the differences in the structure of the parent compounds. Thus, the first molecule of the diamine may begin by reaction with the C-2, in each case followed by either cyclisation with C-1 or C-3. In the present



Scheme 3

case C-3 may be less reactive than C-1 due to its interaction with the C-6 hydroxyl group to form a hemiacetal. Such interaction does not exist in the masked derivatives or in the corresponding methyl[7] or phenyl analogue[18], and consequently the reactivity of C-3 may be anticipated to be competing with that of C-1.

EXPERIMENTAL

Melting points were determined using a "MelTemp" apparatus and are uncorrected. I.r. spectra were recorded on a Unicam SP 1025 spectrophotometer. ^{1}H-N.m.r. spectra were measured with a Varian EM-390 spectrometer using Me_4Si as the internal standard, and chemical shifts are reported on the δ scale. Elemental analyses were performed at the Microanalytical Laboratory, Cairo University.

*6,7-Dimethyl-3-(1-oxo-*D-erythro-*2,3,4-trihydroxybuty)-2[1H]-quinoxalinone* (**4b**). — To a solution of D-erythorbic acid (1.76 g, 10.0 mmol) in water (15 mL) was added *p*-benzoquinone (1.08 g, 10.0 mmol). The mixture was stirred for 1 h at room temperature and then 1,2-diamino-4,5-dimethylbenzene, (1.36 g, 10.0 mmol) was added, and stirring was continued until dissolution was complete. The mixture was then kept overnight, whereby the product (1.47 g, 51%) that formed was collected by filtration and recrystallized from ethanol as colorless needles: m.p. 177–180°; ν_{max} 3360 (OH), 3295 (NH), 1720 (CO), 1660 (OCN), 1630 sh cm^{-1} (C=N); ^{1}H-n.m.r. (DMSO-d_6): δ 2.30 and 2.33 (2s, 6 H, 2 CH_3), 3.00–4.90 and 5.40 (2m, 6 H, Bu, OH), 4.76 and 4.92 (2d, ca. 1 H, $J_{2,3}$ 5.1, 5.7 Hz, H-2), 7.09, 7.12, 7.56 and 7.60 (4s, 2 H, ArH).

Anal. Calc. for $C_{14}H_{16}N_2O_5$: C, 57.5; H, 5.5; N, 9.6. Found: C, 57.3; H, 5.7; N, 9.8.

*6,7-Dimethyl-3-(*D-erythro-*2,3,4-trihydroxybutyl-1-phenylhydrazono)-2[1H]-quinoxalinone*[19] (**5b**). — ^{1}H-n.m.r. (DMSO-d_6): δ 2.30, 2.33 and 2.35 (3s, 6 H, 2 CH_3), 3.00–4.10 (3 m, 5 H, Bu, OH), 4.69 and 5.20 (2d, 1 H, $J_{2,3}$ 6.8, 6.6 Hz, H-2), 6.80, 7.10, 7.44, and 7.60 (2m, 2s, 8 H, ArH).

*2-(2-Amino-4,5-dimethylphenylcarbamoyl)-3-(*D-erythro-*glycerol-1-yl)-6,7-dimethylquinoxaline* (**6**). — A stirred solution of D-erythorbic acid (3.52 g, 20.0 mmol) in water (50 mL) was cooled, and a solution of *p*-benzoquinone (2.16 g, 20.0 mmol) in methanol (50 mL) was added with stirring. The stirring was continued for 20 min at room temperature, and then a solution of 1,2-diamino-4,5-dimethylbenzene (5.44 g, 40.0 mmol) in water (100 mL) was added in one portion of the reaction mixture. After 5 min, the reaction mixture was heated at 40°, and then left at room temperature for 24 h. The product (5.83 g, 71%) that separated out was filtered, washed with water, and recrystallized from acetone–water to give colorless needles: m.p. 213–215°; ν_{max} 3390 (OH), 3260 (NH), 1660 cm^{-1} (OCN); ^{1}H-n.m.r. (DMSO-d_6): δ 2.12 (s, 6 H, 2 CH_3), 2.52 (s, 6 H, 2 CH_3), 3.54 (m, 2 H, H-3,3′), 3.80 (m, 1 H, H-2), 4.30 (t, 1 H, OH), 4.61 (2s, 2 H, NH_2), 5.13 (t, 1 H, H-1), 5.36 (d, 1 H, OH), 6.46, 7.00, 7.76, and 7.81 (4s, 4 H, ArH), and 9.73 (s, 1 H, NH).

Anal. Calc. for $C_{22}H_{26}N_4O_4$: C, 64.4; H, 6.4; N, 13.7. Found: C, 64.0; H, 6.2; N, 13.2.

A solution of the colorless product described in the foregoing (2.0 g, 4.9 mmol) in

methanol (40 mL) was boiled under reflux 30 min, then cooled to 0°, and ether (40 mL) was added. The product (1.29 g, 64%) was found to be a yellow form, with m.p. 213–215° and an i.r. spectrum identical to that of the colorless form.

*2-(2-Acetylamino-4,5-dimethylphenylcarbamoyl)-3-(*D-erythro-*glycerol-1-yl)-6,7-dimethylquinoxaline* (**7**). — A solution of **6** (1.5 g, 3.65 mmol) in *N,N*-dimethylformamide (13 mL) was treated with acetic anhydride (8 mL) and then kept for 7 h at room temperature. Absolute methanol (25 mL) was added, and the product was collected by filtration, washed with water, and dried (1.36 g, 82%). It was recrystallized from ethanol in colorless needles: m.p. 199–201°; ν_{max} 3425 (OH), 3280 (NH), 1655 cm^{-1} (OCN); ^{1}H-n.m.r. (DMSO-d_6): δ 2.11 (s, 3 H, Ac), 2.23, 2.25, 2.52, and 2.53 (4s, 12 H, 4 CH_3), 3.07, 3.65, 3.92, 4.25, and 5.31 (m, 6 H, Bu, OH), 5.50 (d, 1 H, H-1), 7.21, 7.65, 7.86, and 7.91 (4s, 4 H, ArH), 9.37 (s, 1 H, NH).

Anal. Calc. for $C_{24}H_{28}N_4O_5$: C, 63.7; H, 6.2; N, 12.4. Found: C, 63.5; H, 5.9; N, 12.1.

*2-(Acetylamino-4,5-dimethylphenylcarbamoyl)-3-(1,2,3-tri-*O*-acetyl-*D*-erythro-glycerol-1-yl)-6,7-dimethylquinoxaline* (**8**). — To a cold solution of compound **7** (1.50 g, 3.65 mmol) in dry pyridine (15 mL) was added acetic anhydride (12 mL), and the mixture was kept for 2 h at 0° and then for overnight at room temperature. The mixture was then poured onto crushed ice, and the product was collected by filtration, washed repeatedly with water and dried (1.34 g, 74%). It was recrystallized from ethanol to give pale yellow needles: m.p. 165–167°; ν_{max} 3270 (NH), 1750 (OAc), 1665 cm^{-1} (OCN); ^{1}H-n.m.r. ($CDCl_3$): δ 1.90, 1.93, 2.10 and 2.13 (4s, 12 H, 3 OAc, NAc), 2.23 (s, 6 H, 2 CH_3), 2.50 (s, 6 H, 2 CH_3), 4.30 (q, 1 H, $J_{2,3'}$ 6Hz, $J_{3,3'}$ 12.6 Hz, H-3'), 4.55 (q, 1 H, $J_{2,3}$ 3 Hz, H-3), 5.70 (m, 1 H, H-2), 7.10 (d, 1 H, $J_{1,2}$ 6 Hz, H-1), 7.22, 7.36, and 7.76 (3s, 4 H, ArH), 8.00 and 9.73 (2s, 2 H, 2 NH).

Anal. Calc. for $C_{30}H_{34}N_4O_8$: C, 62.3; H, 5.9; N, 9.7. Found: C, 62.0, H, 5.7; N, 9.4.

*3-(*D-erythro-*Glycerol-1-yl)-6,7-dimethylquinoxaline-2-carboxylic acid-γ-lactone* (**10**). — A solution of **6** (2.5 g, 6.09 mmol) in 0.5N hydrochloric acid (40 mL) was cooled and left for 20 h at 5°. The product that separated out was filtered off, successively washed with water, dried (1.15 g, 69%) and recrystallized from ethanol to give colorless needles: m.p. 203–205°; ν_{max} 3300 (OH), 1800 cm^{-1} (OCO); ^{1}H-n.m.r. (DMSO-d_6): δ 2.58 (s, 6 H, 2 CH_3), 3.80 (m, 2 H, H-3,3'), 4.29 (t, 1 H, H-2), 4.61 (s, 1 H, OH), 5.18 (s, 1 H, OH), 5.88 (m, 1 H, H-1), 8.04 and 8.08 (2s, ArH).

Anal. Calc. for $C_{14}H_{14}N_2O_4$: C, 61.3; H, 5.1; N, 10.2. Found: C, 61.7; H, 5.3; N, 10.4.

*3-(2,3-Di-*O*-acetyl-*D*-erythro-glycerol-1-yl)-6,7-dimethylquinoxaline-2-carboxylic acid-γ-lactone* (**9**). — To a cold solution of **10** (1.2 g, 4.38 mmol) in dry pyridine (10 mL) was added acetic anhydride (8 mL). Conventional processing of the reaction mixture as above and recrystallization of the product (1.22 g, 78%) from ethanol gave **9** as colorless needles: m.p. 165–167°; ν_{max} 1770 (OCO), 1745 cm^{-1} (OAc); ^{1}H-n.m.r. ($CDCl_3$): δ 1.93, 2.05 (2s, 6 H, 2 OAc), 2.28 (s, 6 H, 2 CH_3), 4.40 (t, 1 H, H-3'), 4.54 (t, 1 H, H-3), 5.75 (t, 1 H, H-2), 5.84 (d, 1 H, H-1), 7.99, 8.12, (2s, 2 H, ArH).

Anal. Calc. for $C_{18}H_{18}N_2O_6$: C, 60.3; H, 5.1; N, 7.8. Found: C, 60.4; H, 5.4; N, 7.5.

*6,7-Dimethyl-3-(2,3-*O*-isopropylidene-*D*-erythro-glycerol-1-yl)-quinoxaline-2-carboxylic acid-γ-lactone* (**11**). — Compound **10** (0.60 g, 2.19 mmol) was stirred with dry acetone (20 mL) and concentrated sulfuric acid (2 drops) for 2 h. The mixture was stored at room temperature overnight and then neutralised with anhydrous sodium carbonate and filtered, and the inorganic salts were washed with dry acetone. The combined filtrate and washings were concentrated to give the product (0.52 g, 76%) that was crystallized from ethanol as colorless crystals: m.p. 217–219°; ν_{max} 1770 cm^{-1} (OCO); ^{1}H-n.m.r. ($CDCl_3$): δ 1.07 and 1.30 (2s, 6 H, 2 CH_3), 2.53 (s, 6 H, 2 CH_3), 4.20 (m, 2 H, H-3,3'), 4.73 (m, 1 H, H-2), 5.64 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 7.97 and 8.07 (2s, 2 H, ArH).

Anal. Calc. for $C_{17}H_{18}N_2O_4$: C, 65.0; H, 5.8; N, 8.9. Found: C, 64.8; H, 6.1; N, 8.6.

*2-(2-Aminophenylcarbamoyl)-3-(*D*-erythro-glycerol-1-yl)-6,7-dimethylquinoxaline* (**13**). — A solution of compound **4a** (1.32 g, 5.0 mmol) in ethanol (20 mL) was treated with **4b** (0.68 g, 5.0 mmol) and then boiled under reflux for 1 h. The mixture was concentrated, diluted with water, and the product (1.43 g, 75%) was collected by filtration. It was crystallized from ethanol to give **13** as pale yellow crystals: m.p. 197–198°; ν_{max} 3360 (OH), 3250 (NH), 1670 cm^{-1} (OCN); ^{1}H-n.m.r. (DMSO-d_6): δ 2.48 (s, 6 H, 2 CH_3), 3.80, 4.70, 5.30 and 5.60 (4m, glycerolyl-H, NH_2), 6.9 and 7.4 (2 m, 4 H, ArH), 7.90 and 7.93 (2s, 2 H, ArH), 9.97 (s, 1 H, NH); after addition of D_2O, H-1 appeared as 2 d at δ 5.32 ($J_{1,2}$ 7.0 Hz).

Anal. Calc. for $C_{20}H_{22}N_4O_4$: C, 62.8; H, 5.8; N, 14.7. Found: C, 62.5; H, 5.5; N, 14.3.

Acid hydrolysis of (**13**). — A solution of **13** (2.0 g, 3.95 mmol) in 0.5N hydrochloric acid (40 mL) was processed as for compound **6**. The product was crystallized from ethanol to give colorless needles (1.44 g, 62%): m.p. 203–205°, which was identical with **10**. Its acetylation gave colorless needles (2.19 g, 72%): m.p. 165–167°; identical with **9**.

Action of acetone and sulfuric acid on (**13**). — Compound **13** (2.41 g, 1.45 mmol) was stirred with dry acetone (20 mL) and concentrated sulfuric acid (2 drops) for 2 h. Conventional work up and crystallization of the product gave colorless crystals (0.23 g, 70%): m.p. 217–219°; identical with **11**.

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