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Note

Synthesis of *p*-fluorophenylflavazoles from dehydro-D-isoascorbic acid†

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Numerous heterocyclic compounds have been synthesised from carbohydrate precursors[1–3], the chiral centres of which may or may not be retained in building the heterocyclic ring. We now describe the synthesis of *p*-fluorophenylflavazole derivatives from D-isoascorbic acid.

The products of the reaction of D-*erythro*-2,3-hexodiulosono-1,4-lactone (**2**), obtained *in situ* by the reaction of D-isoascorbic acid (**1**) with *p*-benzoquinone, with *o*-phenylenediamine depend on the reaction conditions and the ratio of the reactants[4]. Reaction of **2** with 1 mol of diamine and subsequent reaction with *p*-fluorophenylhydrazine gave 3-[1-(*p*-fluorophenylhydrazono)-D-*erythro*-2,3,4-trihydroxybutyl]-2-quinoxalinone (**3**). A one-pot synthesis of **3** involved a 1:1:2 mixture of **1**, *o*-phenylenediamine, and *p*-fluorophenylhydrazine, with the arylhydrazine acting as oxidising agent and effecting the conversion **1**→**2**. The structure of **3** was inferred from its mode of preparation compared with that of its aryl analogue. It had an i.r. band at 1652 cm^{-1} for O=C-N and, on periodate oxidation, gave 3-[formyl(*p*-fluorophenylhydrazono)methyl]-2-quinoxalinone (**4**), and the structure **3** was deduced as indicated for its phenyl analogue[1–3].

Compounds of type **3** yield flavazoles by the elimination of water between the quinoxalinone ring and the hydrazone residue. Thus, treatment of **3** with boiling, dilute aqueous sodium hydroxide afforded 1-*p*-(fluorophenyl)-3-(D-*erythro*-glycerol-1-yl)flavazole (**5**), which gave a triacetate (**6**) and a tribenzoate (**7**). When a solution of **3** in alkali was treated with methyl sulphate, a monomethyl derivative was obtained to which the structure **8** having an *N*-methyl group was assigned. Compound **8** had an i.r. band at 1635 cm^{-1} (O=C-N) and, on reaction with acetic anhydride, gave the pyrazole acetate **9**, the structure of which was indicated by i.r. and ^{1}H-n.m.r. data (see Experimental).

Another type of heterocyclisation reaction occurred on treatment of **3** with

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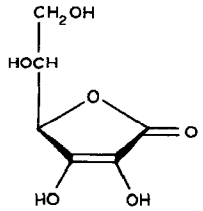

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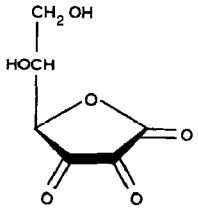

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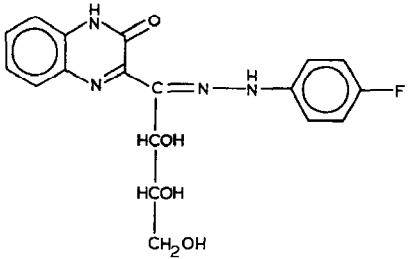

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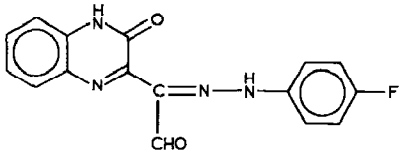

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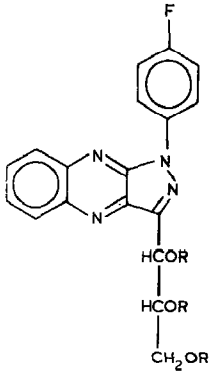
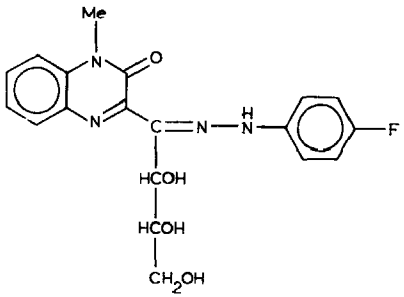


5 R = H

6 R = Ac

7 R = Bz



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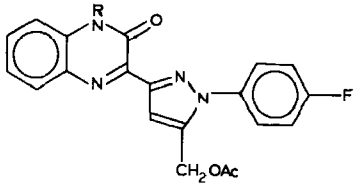

9 R = Me

10 R = H

acetic anhydride, namely, a dehydrative cyclisation to give 3-[5-acetoxymethyl-1-(*p*-fluorophenyl)pyrazol-3-yl]-2-quinoxalinone (**10**), which had i.r. bands at 1750 (OAc) and 1668 cm^{-1} (O=C-N). From these and the ^1H-n.m.r. data (see Experimental), it was concluded that the dehydration had taken place in the glycerol side-chain with simultaneous cyclisation with the hydrazone residue to form a pyrazole ring, as discussed previously[1]. Compound **10** was identical[5] with the product, obtained under similar conditions, from the L-*threo* isomer of **3**.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler-block apparatus and are uncorrected. I.r. spectra were recorded with a Unicam SP 1025 spectrometer, and n.m.r. spectra [for solutions in $(CD_3)_2SO$ or $CDCl_3$, internal Me_4Si] with a Varian EM-390 spectrometer. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University.

*3-[1-(*p*-Fluorophenylhydrazono)-*D*-erythro-2,3,4-trihydroxybutyl]-2-quinoxalinone* (**3**). — A suspension of D-isoascorbic acid (4.4 g, 25 mmol) and *p*-benzoquinone (2.7 g, 25 mmol) in ethanol (40 mL) was stirred for 1.5 h at room temperature and then treated with a solution of *o*-phenylenediamine (2.7 g, 25 mmol) in ethanol (25 mL) and water (125 mL). The mixture was heated to boiling and then treated with a solution of *p*-fluorophenylhydrazine (3.15 g, 25 mmol) in ethanol (15 mL), and boiling was continued for 5–10 min. The orange, crystalline product (6.0 g, 64%) was collected and recrystallised from ethanol to give **3** as orange needles, m.p. 203–204° (dec.); ν_{max}^{KBr} 1652 (OCN), 3340 cm^{-1} (OH).

Anal. Calc. for $C_{18}H_{17}FN_4O_4$: C, 58.1; H, 4.6; N, 15.1. Found: C, 58.0; H, 4.7; N, 14.9.

*3-[Formyl(*p*-fluorophenylhydrazono)methyl]-2-quinoxalinone* (**4**). — A suspension of **3** (2 g, 5.4 mmol) in water (50 mL) was treated with a solution of sodium metaperiodate (2.4 g, 11.2 mmol) in water (15 mL). The mixture was stirred at room temperature for 4 h and then left overnight in the dark. The product (1.5 g, 90%) was collected, washed with water, dried, and crystallised from ethanol to give **4** as dark-orange needles, m.p. 250°; ν_{max}^{KBr} 1650 (OCN), 1675 cm^{-1} (CHO). ^1H-N.m.r. data [$(CD_3)_2SO$]: δ 7.10–7.90 (m, 8 H, Ar), 9.62 (s, 1 H, CHO), 11.20 (s, 1 H, exchangeable with D_2O, NH), 12.63 (s, 1 H, exchangeable with D_2O, NH).

Anal. Calc. for $C_{16}H_{11}FN_4O_2$: C, 61.9; H, 3.6; N, 18.1. Found: C, 62.2; H, 3.4; N, 18.1.

*1-(*p*-Fluorophenyl)-3-(*D*-erythro-glycerol-1-yl)flavazole* (**5**). — A suspension of **3** (5.6 g, 15.1 mmol) in 0.01M sodium hydroxide (300 mL), 1-butanol (30 mL), and methanol (15 mL) was heated under reflux for 1.5 h and then cooled. The precipitate (4.5 g, 85%) was collected, washed with water, dried, and crystallised from ethanol to give **5** as yellow needles, m.p. 241–243° (dec.); ν_{max}^{KBr} 3440 cm^{-1} (OH).

Anal. Calc. for $C_{18}H_{15}FN_4O_3$: C, 61.0; H, 4.2; N, 15.8. Found: C, 61.0; H, 4.4; N, 16.3.

The triacetate **6** of **5** was obtained as yellow needles, m.p. 142–144° (from ethanol); ν_{max}^{KBr} 1750 cm^{-1}(OAc). ^{1}H-N.m.r. data ($CDCl_3$): δ 2.00, 2.03, and 2.23 (3 s, each 3 H, 3 AcO), 4.53 (m, 2 H, CH_2), 6.02 (m, 1 H, H-2), 6.72 (d, *J* 6 Hz, 1 H, H-1), 7.10–8.45 (m, 8 H, Ar).

Anal. Calc. for $C_{24}H_{21}FN_4O_6$: C, 60.0; H, 4.4; N, 11.7. Found: C, 60.1; H, 4.5; N, 11.5.

The tribenzoate **7** of **5** was obtained as yellow needles, m.p. 158–159° (from ethanol); ν_{max}^{KBr} 1726 cm^{-1} (OBz).

Anal. Calc. for $C_{39}H_{27}FN_4O_6$: C, 70.3; H, 4.1; N, 8.4. Found: C, 70.4; H, 4.2; N, 8.4.

*3-[1-(*p*-Fluorophenylhydrazono)-*D*-*erythro*-2,3,4-trihydroxybutyl]-1-methyl-2-quinoxalinone* (**8**). — A suspension of **3** (1 g, 2.7 mmol) in a solution of sodium hydroxide (0.2 g) in aqueous 40% ethanol (25 mL) was heated at ~100° (water bath) until dissolution was complete. Methyl sulphate (1.5 mL) was then added and the mixture was left at room temperature for 10 h with occasional shaking. The product (0.8 g, 78%) was collected, washed with water, dried, and crystallised from ethanol to give **8** as red needles, m.p. 190–191°; ν_{max}^{KBr} 1635 (OCN), 3410 cm^{-1} (OH).

Anal. Calc. for $C_{19}H_{19}FN_4O_4$: C, 59.1; H, 4.9; N, 14.5. Found: C, 58.7; H, 5.1; N, 14.4.

*3-[5-Acetoxymethyl-1-(*p*-fluorophenyl)pyrazol-3-yl]-1-methyl-2-quinoxalinone* (**9**). — A solution of **8** (0.19 g, 0.5 mmol) in acetic anhydride (5 mL) was heated under reflux for 20 min, then cooled, and diluted with ice–water. The product (0.15 g, 77%) was collected, washed with water, dried, and crystallised from ethanol to give **9** as colourless needles, m.p. 218–220°; ν_{max}^{KBr} 1650 (OCN), 1738 cm^{-1} (OAc). ^{1}H-N.m.r. data ($CDCl_3$): δ 2.10 (s, 3 H, AcO), 3.81 (s, 3 H, N-Me), 5.10 (s, 2 H, CH_2O), 7.33, 8.03 (m, d, 9 H, Ar, HC=).

Anal. Calc. for $C_{21}H_{17}FN_4O_3$: C, 64.3; H, 4.4; N, 14.3. Found: C, 64.0; H, 4.4; N, 14.3.

*3-[5-Acetoxymethyl-1-(*p*-fluorophenyl)pyrazol-3-yl]-2-quinoxalinone* (**10**). — A solution of **3** (2 g, 5.4 mmol) in acetic anhydride (30 mL) was heated under reflux for 15 min, cooled, and poured onto crushed ice. The product (1.7 g, 84%) was collected, washed with water, dried, and crystallised from ethanol to give **10** as colourless needles, m.p. 256–258°; ν_{max}^{KBr} 1668 (OCN), 1750 cm^{-1} (OAc). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 2.08 (s, 3 H, AcO), 5.20 (s, 2 H, CH_2O), 7.23–7.87 (m, 9 H, Ar, HC=), 12.60 (bs, 1 H, exchangeable with D_2O, NH).

Anal. Calc. for $C_{20}H_{15}FN_4O_3$: C, 63.5; H, 4.0; N, 14.8. Found: C, 63.6; H, 4.2; N, 14.7.

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