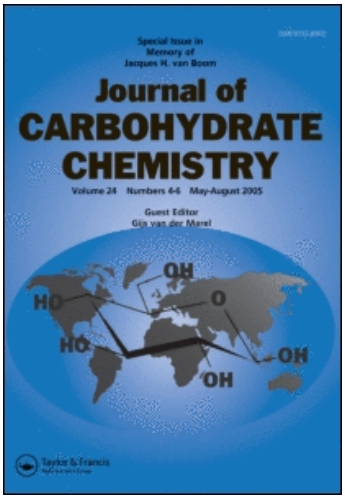

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Symthesis of 3-[1-(p-Fluorophemyl)-Pyrazol-3-YL]-Quimoxalimomes

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SYNTHESIS OF 3-[1-(p-FLUOROPHENYL)-PYRAZOL-3-YL]-QUINOXALINONES[1]

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ABSTRACT

3-[1-(p-Fluorophenylhydrazono)-L-threo-2,3,4-trihydroxybutyl]-2-quinoxalinone was prepared and transformed to 3-[5-acetoxymethyl-1-(p-fluorophenyl)-pyrazol-3-yl]-2-quinoxalinone. N-methylation, followed by dehydrative cyclisation, gave the N-methyl derivative of the latter pyrazole. Periodate oxidation gave a glyoxalyl derivative whose aldehyde functionality was confirmed by reduction and oximation.

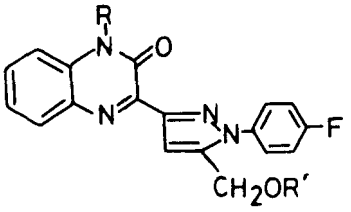
INTRODUCTION

The varied role of heterocyclic compounds in agricultural, medicinal and natural products chemistry has attracted the attention of chemists in finding various approaches for their synthesis. Exploration of reactions of carbohydrate molecules with hydrazines and their conversion into heterocycles are the main goals of our laboratory, whereby successful synthetic approaches for various types of heterocycles have been achieved.[2-4] The importance of organic compounds containing fluorine[5] as insecticides and as biologically active molecules drew our attention to the construction of some nonfused

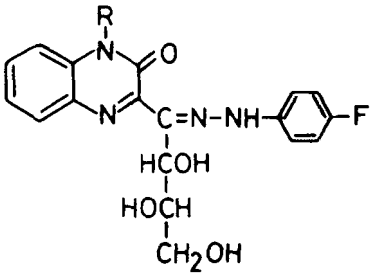
bis(heterocycles) of the pyrazolyl-quinoxaline type which contain fluorine atoms.

RESULTS AND DISCUSSION

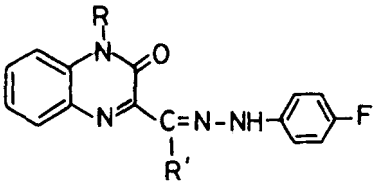
The strategy which was devised for the synthesis of the target compounds utilised L-ascorbic acid as a carbon frame for the heterocyclic rings. Thus the oxidation of L-ascorbic acid affords dehydro-L-ascorbic acid (DHA), which possesses potential reactivity towards reaction with amines and hydrazines.[2] Both C-1 and C-2 of DHA were utilized in constructing a quinoxalinone ring[6] by reaction with a molar equivalent of o-phenylenediamine. The C-3 carbonyl was then reacted with p-fluorophenylhydrazine to give the hydrazone **5**. The structure of



(1) R = Me, R' = Ac
(2) R = Me, R' = H
(3) R = R' = H
(4) R = H, R' = Ac



(5) R = H
(6) R = Me



(7) R = H, R' = CHO
(8) R = Me, R' = CHO
(9) R = H, R' = HC=NOH
(10) R = H, R' = CH_2OH
(11) R = Me, R' = CH_2OH

5 was confirmed, as in the case of the phenyl analog,[2] to be 3-[1-(p-fluorophenylhydrazono)-L-threo-2,3,4-trihydroxybutyl]-2-quinoxalinone. The alternative structure, 2,2'-anhydro-2-hydroxy-2-[1-(p-fluorphenylhydrazono)-L-threo-2,3,4-trihydroxybutyl]quinoxaline was rejected, as the infrared spectrum showed the presence of a band at 1660 cm^{-1} due to the presence of an OCN group, thus agreeing with structure 5. Moreover, the periodate oxidation of 5 gave 3-[1-(p-fluorophenyl-hydrazono)-glyoxal-1-yl]-2-quinoxalinone (7).

The formulation of the reaction product as 5 confirms that the condensation of o-phenylenediamine with DHA gave a 2-quinoxalinone, which reacted with p-fluorophenylhydrazine to give 5. The first step may be occurring via the condensation of the diamine with DHA, which was accompanied by ring opening, or the reaction may have occurred via the open-chain 2,3-dioxo-L-gulonic acid, which is known[2] to exist in equilibrium with DHA in the aqueous solution.

In addition to the above structural aspects, this periodate oxidation provides a simple route to glyoxalyl-quinoxalin-2-one which is of great potential as a precursor for other heterocyclic compounds. Reduction of the aldehyde with sodium borohydride gave the corresponding alcohol, 3-[1-(p-fluorophenylhydrazone)-2-hydroxyethyl]-2-quinoxalinone (10), which lacked the aldehydic band in its infrared spectrum.

Reaction of 7 with hydroxylamine gave the corresponding oxime 9, whose infrared spectrum showed a band at 1685 cm^{-1} (due to OCN).

The action of alkali on 5 gave an intermediate that was not isolated, from which the starting material was readily regenerated upon acidification or it could be heterocyclised to flavazole upon boiling in the alkaline solution. When this intermediate was treated with dimethyl sulfate, a product separated out whose elemental analysis agreed with the molecular formula $C_{19}H_{19}FN_4O_4$, indicating that monomethylation had taken place. Six possible structures could be drawn for such a monomethylated derivative. Structure 6 was the one assigned for the

methylated derivative based upon the following evidence:

i.) The infrared spectrum showed a band at 1665 cm^{-1} (due to the OCN group), indicating the presence of the methyl group on the nitrogen, as in **6**, rather than on the oxygen.

ii.) Periodate oxidation of **6** afforded the aldehyde 3-[1-(p-fluorophenylhydrazono)-glyoxal-1-yl]-1-methyl-2-quinoxalinone (**8**). The infrared spectrum of the aldehyde **8** showed a band at 1680 cm^{-1} (due to the CHO group) in addition to another band at 1660 cm^{-1} (due to the OCN). The presence of the aldehydic group was confirmed by its reduction with sodium borohydride to give 3-[1-(p-fluorophenylhdrazono)-2-hydroxy-ethyl]-1-methyl-2-quinoxalinone (**11**). The infrared spectrum of **11** showed the absence of an aldehydic band, whereas a band appeared at 3350 cm^{-1} due to the hydroxyl group. Isolation of the aldehyde **8**, shown to retain the methyl group, indicated the existence of the methyl on the heterocyclic ring or on the hydrazone residue and not on the glycerol moiety.

iii.) When **6** was boiled with acetic anhydride, a product **1** was obtained whose infrared and ^1H NMR spectra were identical with the product resulting from similar reaction on the D-erythro analog[7] of **6**.

Heating 3-[-(p-fluorophenylhydrazono)-L-threo-2,3,4-trihydroxybutyl]-2-quinoxalinone (**5**) with acetic anhydride afforded the unmethylated pyrazole acetate, 3-[5-(acetoxymethyl)-1-(p-fluorophenyl)-pyrazol-3-yl]-2-quinoxalinone (**4**), which was identical with that obtained from the reaction of acetic anhydride on the D-erythro analog[7] of **5**. The pyrazole acetate **4** showed in its ^1H NMR spectrum two singlets at δ2.15 and 5.15 due to an acetyl and a methylene group, a multiplet at δ7.1-8.15 due to the aromatic protons, and a singlet at δ12.06 due to the NH group. Hydrolysis of the pyrazole acetates **1** and **4** by boiling with aqueous-ethanolic sodium hydroxide, followed by acidification with acetic acid, afforded 3-[1-(p-fluorophenyl)-5-(hydroxymethyl)-pyrazol-3-yl]-1-methyl-2-quinoxalinone (**2**) and 3-[1-(p-fluorophenyl)-5-(hydroxymethyl)-pyrazol-3-yl]-2-quinoxalinone (**3**), respectively. The infrared

spectra of both **2** and **3** showed the absence of the acetyl band of their precursors and the appearance of a hydroxyl band at 3400 and 3480 cm^{-1}, respectively.

EXPERIMENTAL

General Procedures. Melting points were determined with a "Meltemp" apparatus using a 76-mm immersion thermometer and are uncorrected. Infrared (IR) spectra were recorded with a Unicam SP 1025 spectrometer. The ^1H NMR spectrum was determined with a Varian EM-390 spectrometer for a solution in chloroform-*d*. The spectrum is reported with chemical shifts downfield from Me_4Si. Microanalyses were carried out in the Unit of Microanalysis, Faculty of Science, Cairo University, Cairo, Egypt.

3-[1-(p-Fluorophenylhydrazono)-L-threo-2,3,4-trihydroxybutyl]-2-quinoxalinone (5). A suspension of L-ascorbic acid (4.4 g, 25 mmol) and *p*-benzoquinone (2.7 g, 25 mmol) in ethanol (40 mL) was stirred for 90 min at room temperature. The resulting homogeneous, dark-yellow solution was treated with a solution of *o*-phenylenediamine (2.7 g, 25 mmol) in ethanol (25 mL) and water (25 mL) and then heated until boiling. The reaction mixture was then treated with a solution of *p*-fluorophenylhydrazine (3.2 g, 25 mmol) in water (10 mL), and the mixture was boiled for 5-10 min, whereby an orange crystalline product was separated. It was recrystallized from ethanol to give orange crystals of **5** (7.0 g, 75% yield): mp 185 °C; ν_{max}^{KBr} 1660 (OCN), 3215(NH), and 3400(OH) cm^{-1}. Anal. Calcd. for $C_{18}H_{17}FN_4O_4$: C, 58.1; H, 4.6; N, 15.1. Found: C, 57.7; H, 4.5; N, 15.4.

3-[1-(p-Fluorophenylhydrazono)glyoxal-1-yl]-2-quinoxalinone (7). A suspension of **5** (3.72 g, 10 mmol) in water (50 mL) was treated with a solution of sodium meta-periodate (5.4 g, 25 mmol) in water (20 mL). The mixture was stirred at room temperature for 4 h and then left overnight in the dark. The product was filtered, washed with water, and crystallized from ethanol to give orange crystals of **7** (2.7 g, 87%

yield): mp 250 °C (lit.[7] mp 250 °C). Anal. Calcd. for $C_{16}H_{11}FN_4O_2$: C, 61.9; H, 3.6; N, 18.1. Found: C, 61.6; H, 3.7; N, 17.5.

3-[1-(p-Fluorophenylhydrazono)-2-hydroxyethyl]-2-quinoxalinone (10). A solution of **7** (0.52 g, 1.7 mmol) in a mixture of N,N-dimethylformamide (15 mL) and methanol (10 mL) was treated with sodium borohydride (0.7 g). The mixture was stirred at room temperature for 2 h and then left standing for an additional 4 h. The reaction mixture was diluted with water, and the precipitate was filtered, washed with water, and dried. It was recrystallized from ethanol go give red crystals of **10** (0.48 g, 90% yield): mp 236 °C; ν_{max}^{KBr} 1660 (OCN) and 3500 (OH) cm^{-1}. Anal. Calcd. for $C_{16}H_{13}FN_4O_2$: C, 61.5; H, 4.2; N, 17.9. Found: C, 61.5; H, 4.5; N, 17.5.

3-[1-(p-Fluorophenylhydrazono)-2-oxime-glyoxal-1-yl]-2-quinoxalinone (9). A solution of **7** (0.3 g, 1 mmol) in ethanol (10 mL) containing a few drops of N,N-dimethylformamide was treated with hydroxylamine hydrochloride (0.1 g, 1 mmol) and sodium acetate (0.16 g, 1 mmol). The reaction mixture was heated on a boiling water bath for few min, and the product which separated was recrystallized from ethanol (0.28 g, 89% yield): mp 272 °C; ν_{max}^{KBr} 1685 (OCN) and 3500 (OH) cm^{-1}. Anal. Calcd. for $C_{16}H_{12}FN_5O_2$: C, 59.1; H, 3.7; N, 21.5. Found C, 58.8; H, 3.9; N, 21.0.

3-[1-(p-Fluorophenylhydrazono)-L-threo-2,3,4-trihydroxybutyl]-1-methyl-2-quinoxalinone (6). A suspension of **5** (0.372 g, 1 mmol) in a solution of sodium hydroxide (0.2 g) in 40% aqueous ethanol (25 mL) was heated on a water bath until dissolution had taken place. Dimethyl sulfate (0.5 mL) was then added, and the mixture was left at room temperature for 10 h, with occasional shaking. The product that separated out was filtered, washed with water, and recrystallized from ethanol to give orange crystals of **6** (0.26 g, 70% yield): mp 225 °C; ν_{max}^{KBr} 1665 (OCN) and 3400 (OH) cm^{-1}. Anal. Calcd. for $C_{19}H_{19}FN_4O_4$: C, 59.1; H, 5.0; N, 14.5. Found: C, 58.7; H, 5.3; N, 14.8.

3-[1-(p-Fluorophenylhydrazono)glyoxal-1-yl]-1-methyl-2-quinoxalinone (8). A suspension of **6** (3.85 g, 1 mmol) in water (50 mL) was treated with a solution of sodium metaperiodate (5.4 g, 25 mmol) in water (20 mL). The reaction mixture was stirred at room temperature for 4 h and then left overnight in the dark. The product which separated was filtered, washed with water, and recrystallized from ethanol to give orange crystals of **8** (2.8 g, 86% yield): mp 240 °C; ν_{max}^{KBr} 1660 (OCN) and 1680 (CHO) cm^{-1}. Anal. Calcd. for $C_{17}H_{13}FN_4O_2$: C, 63.0; H, 4.0; N, 17.3. Found: C, 63.0; H, 4.5; N, 17.2.

3-[1-(p-Fluorophenylhydrazono)-2-hydroxyethyl]-1-methyl-2-quinoxalinone (11). A solution of **8** (0.65 g, 2.0 mmol) in a mixture of N,N-dimethylformamide (15 mL) and methanol (10 mL) was treated with sodium borohydride (10.7 g). The mixture was stirred at room temperature for 2 h and then allowed to stand for an additional 4 h. The reaction mixture was diluted with water, and the precipitate was filtered, washed with water, and dried. It was recrystallized from ethanol to give orange crystals of **11** (0.5 g, 76% yield): mp 122 °C; ν_{max}^{KBr} 1655 and 1665 (OCN) and 3350 (OH) cm^{-1}. Anal. Calcd. for $C_{17}H_{15}FN_4O_2$: C, 62.6; H, 4.6; N, 17.2. Found: C, 62.3; H, 4.2; N, 17.2.

3-[5-(Acetoxymethyl)-1-(p-fluorophenyl)-pyrazol-3-yl]-1-methyl-2-quinonxalinone (1). A solution of 6 (0.19 g, 0.5 mmol) in acetic anhydride (5 mL) was heated under reflux for 15 min. The mixture was allowed to cool, diluted with ice cold water, and the product that separated out was filtered, washed sequentially with water and ethanol, and dried. It was recrystallized from ethanol to give colourless needles of **1** (0.13 g, 67% yield): mp 222 °C (lit.[7] mp 218-220 °C). Anal. Calcd. for $C_{21}H_{17}FN_4O_3$: N, 14.3. Found: N, 14.5.

3-[5-(Acetoxymethyl)-1-(p-fluorophenyl)-pyrazol-3-yl]-2-quinoxalinone (4). A solution of 5 (1.8 g, 4.8 mmol) in acetic anhydride (5 mL) was heated under reflux for 15 min, and the mixture was cooled and poured onto crushed ice. The product that separated was filtered,

washed with water, and dried. It was recrystallized from ethanol to give colourless needles of **4** (1.6 g, 85% yield): mp 258 °C (lit.[7] mp 256-258 °C); ν_{max}^{KBr} 1665 (OCN) and 1750 (OAc) cm^{-1}; ^1H NMR ($CDCl_3$): δ 12.06 (s, 1H, NH), 8.15 and 7.1 (d and m, 9H, aromatic protons), 5.15 (s, 2H, CH_2O), 2.15 (s, 3H, CH_3CO); the singlet at δ12.06 disappeared upon addition of D_2O. Anal. Calcd. for $C_{20}H_{15}FN_4O_3$: N, 14.8. Found: N, 14.8.

Hydrolysis of 3-[5-(acetoxymethyl)-1-(p-fluorophenyl)-pyrazol-3-yl]-1-methyl-2-quinoxalinone (1). A solution of **1** (0.4 g) and NaOH (0.4 g) in 1:1 water-ethanol (10 mL) was boiled under reflux for 4 h. The mixture was cooled and then acidified with acetic acid, and the product that separated out was filtered and washed sequentially with water and ethanol. It was recrystallized from ethanol to give colourless needles of pure **2** (0.25 g, 70% yield): mp 245 °C; ν_{max}^{KBr} 1670 (OCN) and 3400 (OH) cm^{-1}. Anal. Calcd. for $C_{19}H_{15}FN_4O_2$: C, 65.1; H, 4.3; N, 16.0 Found: C, 65.1; H, 4.0; N, 15.9.

Hydrolysis of 3-[5-(acetoxymethyl)-1-(p-fluorophenyl)-pyrazol-3-yl]-2-quinoxalinoe (4). A solution of **4** (0.4 g) and NaOH (0.4 g) in 1:1 water-ethanol (10 mL) was boiled under reflux for 4 h. The mixture was cooled and acidified with acetic acid, and the product that separated out was filtered, washed sequentially with water and ethanol, and dried. It was recrystallized from ethanol to give colourless needles of **3** (0.25 g, 70% yield): mp 280 °C; ν_{max}^{KBr} 1670 (OCN) and 3480 (OH) cm.$^{-1}$ Anal. Calcd. for $C_{18}H_{13}FN_4O_2$: C, 64.3; H, 3.9; N, 16.7. Found: C, 64.2; H, 4.1; N, 16.7.

REFERENCES

1. Heterocycles from Carbohydrate precursors, Part 38. For Part 37, see preceeding paper.

2. E. S. H. El Ashry in, "Nitrogen Derivatives of Ascorbic Acid", in "Ascorbic acid: Chemistry, Metabolism and Uses", P. A. Seib and B. M. Tolbert, Eds., Advances in Chemistry Series, Vol. 200, American Chemical Society, Washington, DC, 1982.

3. E. S. H. El Ashry, Y. El Kilany, A. A. Abdallah, and K. Mackawy, Carbohydr. Res., 113, 273 (1983).

4. E. S. H. El Ashry, N. Rashed, and A. Mousaad, Carbohydr. Res., 100, C39 (1982).

5. A. A. E. Penglis, Adv. Carbohydr. Chem. Biochem., 38, 195 (1981).

6. E. S. H. El Ashry, I. E. El Kholy and Y. El Kilany, Carbohydr. Res., 60, 303 (1978); 60, 396 (1978).

7. E. S. H. El Ashry, M. Abdel Rahman, G. H. Labib, A. El-Massry, and A. Mofti, Carbohydr. Res., 152, 339 (1986).