Carbohydrate Research, 64 (1978) 81–88

REACTIONS OF 3-(1-ARYLHYDRAZONO-L-*threo*-2,3,4-TRIHYDROXYBUTYL)-1-METHYL-2-QUINOXALINONES*

EL SAYED H. EL ASHRY**, IBRAHIM E. EL KHOLY, AND YELDEZ EL KILANY
Chemistry Department, Faculty of Science, Alexandria University, Alexandria (Egypt)
(Received September 21st, 1977; accepted for publication, November 9th, 1977)

ABSTRACT

The 1-methyl derivatives (**3** and **4**) of 3-(1-phenyl- (**1**) and 3-(1-*p*-bromophenylhydrazono-L-*threo*-2,3,4-trihydroxybutyl)-2-quinoxalinone (**2**) were prepared by methylation. Periodate oxidation of **3** gave 1-methyl-3-[1-(phenylhydrazono)glyoxal-1-yl]-2-quinoxalinone (**5**), which, on reduction with sodium borohydride, gave the corresponding 3-[2-hydroxy-1-(phenylhydrazono)ethyl] derivative (**8**). Reaction of **5** with hydroxylamine or benzoylhydrazine gave the corresponding 2-oxime (**6**) and 2-(benzoylhydrazone) (**7**), respectively. Acetic anhydride causes one molecule of **3** or **4** to undergo elimination of two molecules of water, with simultaneous acetylation and ring closure to afford pyrazoles **9** and **10**, respectively. Pyrolysis of the triacetate of **3** led to the elimination of acetic acid from the sugar and the hydrazone residue, to give the 3-[5-(acetoxymethyl)-1-phenylpyrazol-3-yl] derivative (**9**). Acetic acid was found to effect the same rearrangement, but without acetylation, of **1**, **2**, and **3** to give the 3-[5-(hydroxymethyl)] derivatives **11**, **12**, and **13**, respectively. The structure of these pyrazoles was confirmed by a series of reactions, including methylation and acetylation. The n.m.r. and i.r. spectra of the compounds were investigated.

INTRODUCTION

Continuing our work on the synthesis of nitrogen heterocyclic compounds in the carbohydrate series[1–4], we have described[1,5] the reaction of L-ascorbic acid with *o*-phenylenediamine and arylhydrazines. The reaction products were formulated as acyclic structures[5], 3-(1-arylhydrazono-L-*threo*-2,3,4-trihydroxybutyl)-2-quinoxalinones, rather than as the previously reported[6] cyclic structures, such as 2,2′-anhydro-[2-hydroxy-3-(1-phenylhydrazono-L-*threo*-2,3,4-trihydroxybutyl)quinoxaline] for the phenyl derivative. We have found that these products can undergo a variety of rearrangements leading to different types of heterocyclic compounds[1,5]. It became interesting to study the behavior of similar compounds that are presumably incapable of existence in a cyclic form, namely, the title compounds (**3** and **4**). These have been

*Heterocycles from Carbohydrate Precursors. Part VIII. For Part VII, see ref. 1.
**To whom enquiries should be addressed.

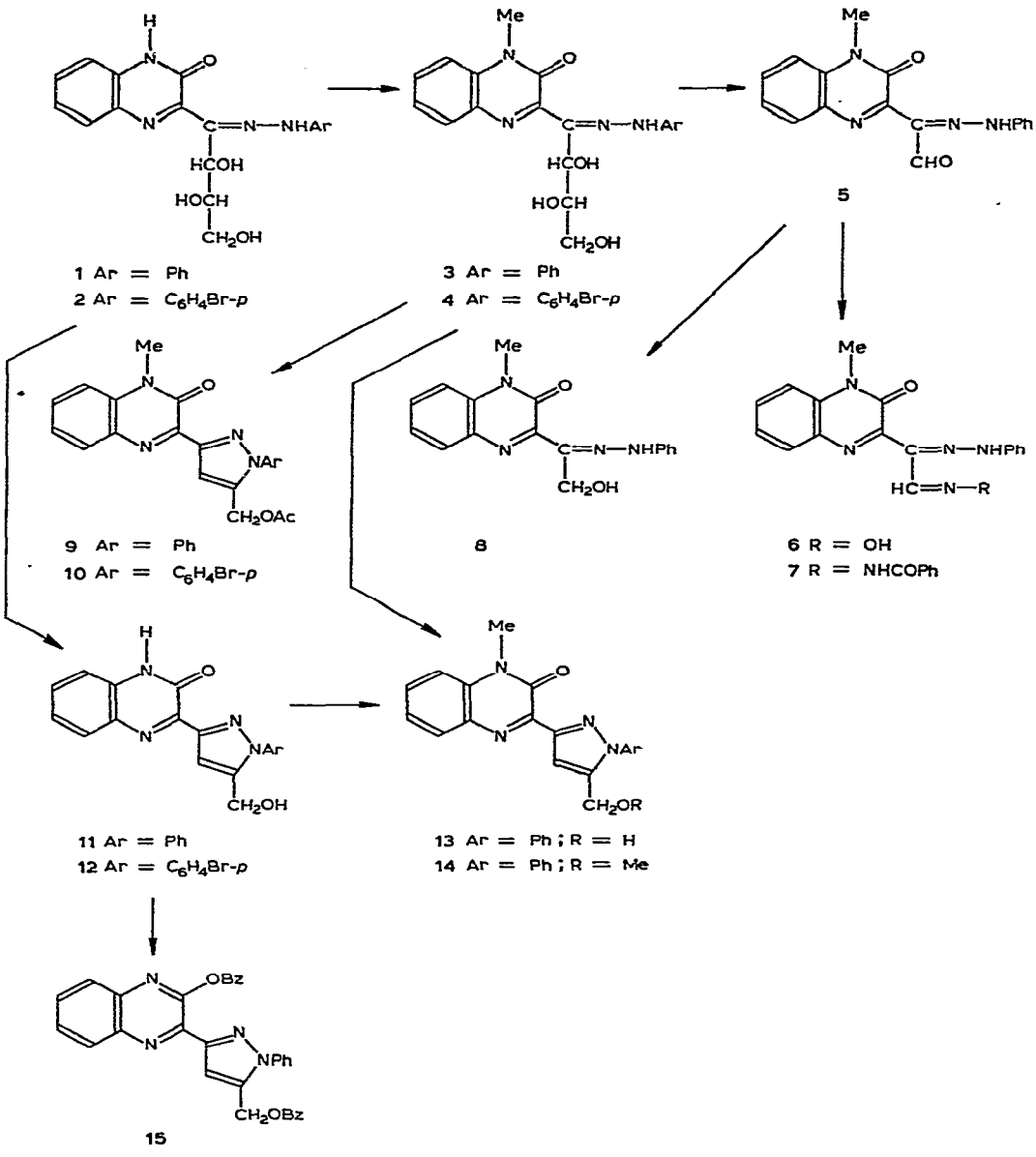
prepared, and their structures confirmed. A study of their versatility as precursors to other heterocyclic compounds is now reported.

DISCUSSION AND RESULTS

Unimolar methylation of 3-(1-phenylhydrazono-L-*threo*-2,3,4-trihydroxybutyl)-2-quinoxalinone (**1**) with dimethyl sulfate in sodium hydroxide was reported[6] by Henseke and Dittrich to give the 1-*N*-methyl derivative **3**. Similarly, we prepared 3-(1-*p*-bromophenylhydrazono-L-*threo*-2,3,4-trihydroxybutyl)-1-methyl-2-quinoxalinone (**4**) from **2**. When the methylation was performed by reaction of methyl iodide with the silver salt of **1**, the same methylated derivative **3** was obtained. The elemental analysis of **3** and **4** showed the presence of only one methyl group in the methylation products. That **3** and **4** have the methyl group on the heterocyclic, rather than an acyclic, nitrogen atom, or the alcoholic oxygen atom, was shown by the following evidence. The infrared (i.r.) spectra of **3** and **4** showed a band at 1645–1640 cm^{-1} due to the OCN group, confirming that the methylation product is an *N*-methyl, not an *O*-methyl (on the heterocyclic ring) derivative. Moreover, the n.m.r. spectrum of **3** showed a signal that resonated as a singlet of three-proton intensity at δ 3.36 for the methyl group, concordant with the assignment based on the i.r. data; two quartets appeared at δ 4.40–4.56 and 4.84–5.00 due to H-4,4′; two doublets, at δ 5.92–5.98 and 6.22–6.28, due to H-3; a doublet at δ 6.90 due to H-2; and a multiplet at δ 7.00–7.88 due to the aromatic protons.

Confirmation that the methylation did not occur on the alditol part was deduced from the periodate oxidation of **3**, which gave a product formulated as 1-methyl-3-(1-phenylhydrazonoglyoxal-1-yl)-2-quinoxalinone (**5**). Its elemental analysis agreed with the molecular formula $C_{17}H_{14}N_4O_2$, and its i.r. spectrum showed, in addition to the OCN group at 1640 cm^{-1}, an aldehyde group at 1680 cm^{-1}. The n.m.r. spectrum of **5** showed a singlet of three-proton intensity at δ 3.26, indicating that the periodate-oxidation product still retained the methyl group. Reaction of **5** with hydroxylamine gave the corresponding oxime (**6**), and reaction with benzoylhydrazine gave 3-[2-(benzoylhydrazono)-1-(phenylhydrazono)-glyoxal-1-yl]-1-methyl-2-quinoxalinone (**7**). These showed in their i.r. spectra the OCN band at 1660–1640 cm^{-1}. The n.m.r. spectrum of **7** showed a singlet at δ 3.32 due to the methyl group, in addition to the aromatic protons at δ 6.80–8.00. Reduction of **5** with sodium borohydride gave 3-[2-hydroxy-1-(phenylhydrazono)ethyl]-1-methyl-2-quinoxalinone (**8**), which lacked the aldehydic band that appeared in the i.r. spectrum of its precursor.

When the orange-colored methyl derivatives **3** and **4** were boiled with acetic anhydride, they afforded colorless products (**9** and **10**, respectively), whose i.r. spectra showed the presence of an acetyl band at 1740 cm^{-1}, in addition to the OCN band at 1660 cm^{-1}. The n.m.r. spectrum of **9** showed three singlets (with intensities having the ratios 3:3:2) at δ 2.08, 3.80, and 5.12, respectively due to an acetyl, a methyl, and a methylene group; the aromatic protons appeared as a multiplet and a quartet,



at δ 7.24–7.68 and 8.00–8.10, respectively. These results indicated that elimination of two molecules of water from one molecule of **3**, and **4**, occurred during the acetylation, to give **9** and **10**, respectively. This formulation was supported by an acceptable elemental analysis. The formation of the pyrazole ring during the acetylation was confirmed by deacetylation and subsequent methylation of **9**, to give 3-[5-(methoxymethyl)-1-phenylpyrazol-3-yl]-1-methyl-2-quinoxalinone (**14**). The latter was found to be identical with the product obtained by the methylation of **11**. The n.m.r.

spectrum of **14** showed two singlets (of three-proton intensity each) at δ 3.34 and 3.62, due to the two methyl groups, in addition to a singlet at δ 4.48 due to the methylene group, and the multiplets at δ 7.22–7.60 and 7.92–8.20 due to the aromatic protons. Dehydration in the alditol part adjacent to a hydrazone residue, with simultaneous ring-closure to the pyrazole, during acetylation with boiling acetic anhydride, has also been noted for other types of compounds[5,7–10], although the reaction is not general, as acetylation of sugar arylhydrazones[11,12], *e.g.*, D-galactose arylhydrazones, with acetic anhydride under reflux gave the penta-*O*-acetyl-*N*-acetyl arylhydrazone derivative.

Pyrolysis of the acetate of **3** was found to occur readily, affording a product **9** identical to that obtained by the action of boiling acetic anhydride on **3**.

In the present work, we have found that such acids as acetic acid cause similar dehydrative cyclization of **3**, to give a colorless product (**13**) whose elemental analysis agreed with the molecular formula $C_{19}H_{16}N_4O_2$. Its n.m.r. spectrum showed two singlets, of three- and two-proton intensity, at δ 3.58 and 5.00, due to a methyl and a methylene group, respectively, indicating the absence of contiguous protons present in the alditol part of its precursor **3**. Similar results were also obtained when **1** was subjected to the action of acetic acid; it gave a colorless product, identified as 3-[5-(hydroxymethyl)-1-phenylpyrazol-3-yl]-2-quinoxalinone (**11**), whose n.m.r. spectrum showed a singlet for the methylene group at δ 5.02 that disappeared on oxidation of **11** with potassium permanganate.

Methylation of **11** with dimethyl sulfate in sodium hydroxide solution, or with methyl iodide and silver oxide, gave the same dimethyl derivative, formulated as 3-[5-(methoxymethyl)-1-phenylpyrazol-3-yl]-1-methyl-2-quinoxalinone (**14**).

That the methylation of **1** gave only a monomethyl derivative **3**, whereas **11** gave the dimethyl derivative **14**, could be explained in the former case by insolubility, in the reaction medium, of the monomethyl derivative, which immediately started to separate upon addition of the dimethyl sulfate. On the other hand, methylation of **11** occurred immediately at the readily accessible position of the heterocyclic ring, to give, at first, a monomethyl derivative that was presumably of higher solubility, allowing it to be present in the solution until further reaction with the methylating agent occurred, to give the more-insoluble product **14**.

Benzoylation of **11** with benzoyl chloride in pyridine, or by the Schotten–Baumann method, gave the same product (**15**), whose elemental analysis agreed with the presence of two benzoyl groups. Formulation as a di-*O*-benzoyl derivative, rather than an *N*-benzoyl-*O*-benzoyl derivative, was deduced from the i.r. spectrum, which showed two bands, at 1725 and 1700 cm^{-1} (due to OBz), and the band at 1660 cm^{-1} (due to OCN) had disappeared.

From the foregoing results, it appears that elimination of two molecules of water from the alditol part and the imino proton of the hydrazone residue in compounds **1–4** occurred readily, to form the pyrazole ring. This could be achieved by acetic acid and acetic anhydride, as well as by dehydration of the acetate of **3**.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler-block apparatus and are uncorrected. I.r. spectra were recorded with Unicam SP 200 and Pye Unicam 1025 spectrometers, and n.m.r. spectra (for solutions in pyridine-d_5, chloroform-*d*, or dimethyl sulfoxide-d_6) with a Joel 100 spectrometer, with tetramethylsilane as the standard. Chemical shifts are given on the δ scale. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

*1-Methyl-3-(1-phenylhydrazono-*L*-threo-2,3,4-trihydroxybutyl)-2-quinoxalinone* (**3**). — Compound **1** (3.5 g) was treated with a solution of sodium hydroxide (2 g) in 40% aqueous ethanol (250 mL), and heated on a steam-bath until dissolution occurred. Dimethyl sulfate (3.5 mL) was then added, and the mixture was kept for 10 h at room temperature. The product that separated was filtered off, washed with water, and recrystallized from ethanol, to give orange needles, yield 50%; m.p. 189–192° (lit.[6] m.p. 186°); ν_{max}^{Nujol} 3500 (OH) and 1640 cm^{-1} (OCN); p.m.r. (C_5D_5N): δ 3.36 (s, 3, N-Me), 4.4–4.56 and 4.84–5.00 (2 q, 2, H-4,4'), 5.92–5.98 and 6.22–6.28 (2 d, 1, H-3), 6.9 (d, 1, H-2), and 7.00–7.88 (m, 9, Ar).

Anal. Calc. for $C_{19}H_{20}N_4O_4$ (368.38): C, 61.9; H, 5.5; N, 15.2. Found: C, 61.6; H, 5.5; N, 15.0.

*3-(1-p-Bromophenylhydrazono-*L*-threo-2,3,4-trihydroxybutyl)-1-methyl-2-quinoxalinone* (**4**). — Compound **2** (4.3 g) in a solution of sodium hydroxide in aqueous methanol was methylated similarly. The product was recrystallized from ethanol, to give orange needles, yield 60%; m.p. 190; ν_{max}^{Nujol} 1645 cm^{-1} (OCN).

Anal. Calc. for $C_{19}H_{19}BrN_4O_4$ (447.29): C, 51.0; H, 4.3; N, 12.5. Found: C, 51.1; H, 4.5; N, 12.8.

1-Methyl-3-[1-(phenylhydrazono)glyoxal-1-yl]-2-quinoxalinones (**5**). — A suspension of **3** (0.37 g) in water (10 mL) was treated with a solution of sodium metaperiodate (0.45 g) in water (10 mL). The mixture was stirred for 2 h at room temperature and then kept overnight. The solid was filtered off, washed with water, and recrystallized from ethanol, to give orange needles, yield 90%; m.p. 198–200°; ν_{max}^{Nujol} 1680 (CHO) and 1640 cm^{-1} (CON); p.m.r. (C_5D_5N): δ 3.26 (s, 3, N-Me), and 6.90–7.60 and 7.90–8.00 (2 m, 10, Ar + =CH).

Anal. Calc. for $C_{17}H_{14}N_4O_2$ (306.31): C, 66.7; H, 4.6; N, 18.3. Found: C, 66.6; H, 4.8; N, 18.6.

1-Methyl-3-(1-phenylhydrazonoglyoxal-1-yl)-2-quinoxalinone 2-oxime (**6**). — A solution of compound **5** (0.3 g) in ethanol (10 mL) and a few drops of *N,N*-dimethylformamide was treated with hydroxylamine hydrochloride (0.1 g) and sodium acetate, and then heated for few minutes, and the product was recrystallized from ethanol, yield 70%; m.p. 203°; ν_{max}^{Nujol} 1640 cm^{-1} (OCN).

Anal. Calc. for $C_{17}H_{15}N_5O_2$ (321.33): C, 63.5; H, 4.7; N, 21.8. Found: C, 63.3; H, 4.5; N, 22.0.

3-[2-(Benzoylhydrazono)-1-(phenylhydrazono)glyoxal-1-yl]-1-methyl-2-quinox-

alinone (7). — A solution of **5** (0.3 g) in ethanol (10 mL) was treated with benzoylhydrazine (0.15 g), heated for a few minutes, and then diluted with water. The product was recrystallized from ethanol, to give yellow needles, yield 80%; m.p. 230°; ν_{max}^{Nujol} 1660 and 1640 cm^{-1} (OCN); p.m.r. (Me_2SO-d_6): δ 3.64 (s, 3, N-Me) and 6.8–8.0 (m, 10, Ar + =CH).

Anal. Calc. for $C_{24}H_{20}N_6O_2$ (424.45): C, 67.9; H, 4.8; N, 19.8. Found: C, 67.6; H, 5.1; N, 19.9.

3-[2-Hydroxy-1-(phenylhydrazono)ethyl]-1-methyl-2-quinoxalinone (**8**). — A solution of compound **5** (0.3 g) in a mixture of *N,N*-dimethylformamide (5 mL) and methanol (5 mL) was treated with sodium borohydride (0.05 g). The mixture was stirred for 2 h at room temperature, kept for a further 4 h, and then diluted with water. The product was recrystallized from ethanol, to give yellow needles, yield 65%; m.p. 188–190°; ν_{max}^{Nujol} 1640 cm^{-1} (OCN).

Anal. Calc. for $C_{17}H_{16}N_4O_2$ (308.3): C, 66.2; H, 5.2; N, 18.2. Found: C, 66.6; H, 5.0; N, 18.6.

3-[5-(Acetoxymethyl)-1-phenylpyrazol-1-yl]-3-methyl-2-quinoxalinone (**9**). — (*Method a*). A suspension of compound **3** (1 g) in acetic anhydride (15 mL) was heated under reflux for 5 min, and the mixture was cooled, and poured onto crushed ice. The product crystallized from ethanol in colorless needles, yield 80%; m.p. 205–206°; ν_{max}^{Nujol} 1740 (OAc) and 1660 cm^{-1} (OCN); p.m.r. ($CDCl_3$): δ 2.08 (s, 3, OC-Me), 3.8 (s, 3, N-Me), 5.12 (s, 2, CH_2), and 7.24–7.68 and 8.00–8.10 (m, and q, 10, Ar + =CH).

Anal. Calc. for $C_{21}H_{18}N_4O_3$ (374.39): C, 67.4; H, 4.9; N, 15.0. Found: C, 67.7; H, 4.6; N, 15.3.

(*Method b*). A solution of compound **13** (0.1 g) in pyridine (5 mL) was treated with acetic anhydride (2 mL), and the mixture was kept for 24 h at room temperature and then processed as usual. The product was recrystallized from ethanol, to give colorless needles, identical with the compound obtained by method *a*.

(*Method c*). The acetate of compound **3** (0.1 g) in a dry test-tube was heated above its melting point for 2 h. The residue was cooled, and crystallized from ethanol in colorless needles, yield 85%; it was identical with the compound obtained by method *a*.

3-[5-(Acetoxymethyl)-1-(p-bromophenyl)pyrazol-3-yl]-1-methyl-2-quinoxalinone (**10**). — Compound **4** was boiled with acetic anhydride as for **9**, and the product crystallized from ethanol in colorless needles, yield 85%; m.p. 235°; ν_{max}^{Nujol} 1735 (OAc) and 1650 cm^{-1} (OCN).

Anal. Calc. for $C_{21}H_{17}BrN_4O_3$ (453.29): C, 55.6; H, 3.8; N, 12.4. Found: C, 55.3; H, 4.1; N, 12.6.

3-[5-(Hydroxymethyl)-1-phenylpyrazol-3-yl]-1-methyl-2-quinoxalinone (**13**). — Compound **3** (1 g) was dissolved in hot acetic acid (10 mL), and the solution was boiled for a further 2 min, and then diluted with water to incipient turbidity. The product crystallized from aqueous ethanol in colorless needles, yield 50%; m.p. 197–199°; ν_{max}^{Nujol} 3450 (OH), 1660, and 1645 cm^{-1} (OCN); p.m.r. (C_5D_5N): δ 3.58 (s, 3, N-Me), 5.00 (s, 2, CH_2), and 7.16–8.16 (m, 10, Ar + =CH).

Anal. Calc. for $C_{19}H_{16}N_4O_2$ (332.35): C, 68.7; H, 4.9; N, 16.9. Found: C, 68.4; H, 4.6; N, 16.7.

3-[5-(Hydroxymethyl)-1-phenylpyrazol-3-yl]-2-quinoxalinone (**11**). — Compound **1** was treated with acetic acid as for the synthesis of **13**. The product was crystallized from ethanol–water, yield 55%; m.p. 249–252° (lit.[6] m.p. 255°, lit.[5] m.p. 250–252°); p.m.r. (C_5D_5N): δ 5.02 (s, 2, CH_2), and 7.24–7.60 and 8.14–8.28 (2 m, 10, Ar + =CH).

3-[1-(p-Bromophenyl)-5-(hydroxymethyl)pyrazol-3-yl]-2-quinoxalinone (**12**). — Compound **2** was treated with acetic acid as for the synthesis of **11**. The product was crystallized from ethanol–water, yield 60%; m.p. 278–280° (lit.[5] m.p. 278–280°).

3-[5-(Methoxymethyl)-1-phenylpyrazol-3-yl]-1-methyl-2-quinoxalinone (**14**). — (*Method a*). A solution of **11** (0.3 g) in methanol (10 mL) was treated with a solution of 0.2M sodium hydroxide (20 mL) and dimethyl sulfate (0.5 mL). The mixture was kept for 3 h at room temperature, and the precipitated product was filtered off, washed with water, and recrystallized from ethanol–water, to give colorless needles, yield 85%; m.p. 174°; ν_{max}^{Nujol} 1645 cm^{-1} (OCN); p.m.r. (C_5D_5N): δ 3.30 (s, 3, O-Me), 3.62 (s, 3, N-Me), 7.22–7.60 and 7.92–8.20 (2 m, 10, Ar + =CH).

Anal. Calc. for $C_{20}H_{18}N_4O_2$ (346.4): C, 69.4; H, 5.2; N, 16.2. Found: C, 69.6; H, 4.9; N, 16.3.

(*Method b*). A solution of **11** (0.3 g) in acetone (10 mL) was treated with a methanolic solution of sodium hydroxide (0.1 g), and then a solution of silver nitrate (0.4 g) in distilled water was added dropwise. The black precipitate of the silver salt was filtered off, washed with methanol, and dried. The dried product was ground up, covered with methyl iodide, the suspension refluxed on a water-bath for 6 h, followed by filtration while hot, and the solid washed with methanol. The combined filtrate and washings were evaporated, and the product was recrystallized from methanol, to give colorless needles, identical with those obtained as in *a*.

2-Benzoyloxy-3-[5-(benzoyloxymethyl)-1-phenylpyrazol-3-yl]quinoxaline (**15**). — (*Method a*). A solution of **11** (0.1 g) in pyridine (5 mL) was treated with benzoyl chloride (0.5 mL) and kept overnight at room temperature. The mixture was then poured onto crushed ice, and the product was filtered off, washed with water, and recrystallized from benzene–ethanol, to give colorless needles, m.p. 153°; ν_{max}^{Nujol} 1725 and 1700 cm^{-1} (OBz); p.m.r. ($CDCl_3$): δ 5.32 (s, 2, CH_2), and 7.14–8.28 (m, 20, Ar + =CH).

Anal. Calc. for $C_{32}H_{22}N_4O_4$ (526.5): C, 73.0; H, 4.2; N, 10.6. Found: C, 72.9; H, 3.7; N, 10.4.

(*Method b*). A solution of **11** (0.5 g) in 2M sodium hydroxide solution (15 mL) was treated with benzoyl chloride (2 mL), and the mixture was shaken for 1 h. The solid that separated was filtered off, washed with water, and recrystallized from ethanol, giving **15**, identical with that obtained by method *a*.

REFERENCES

1 E. S. H. El Ashry, I. E. El Kholy, and Y. El Kilany, *Carbohydr. Res.*, 60 (1978) 396–399.
2 E. S. H. El Ashry and Y. El Kilany, *Chem. Ind. (London)*, (1976) 372–373.

3 E. S. H. EL ASHRY, *Carbohydr. Res.*, 33 (1974) 178–185.
4 E. S. H. EL ASHRY, Y. EL KILANY, AND F. SINGAB, *Carbohydr. Res.*, 56 (1977) 93–104.
5 E. S. H. EL ASHRY, I. E. EL KHOLY, AND Y. EL KILANY, *Carbohydr. Res.*, 60 (1978) 303–314.
6 G. HENSEKE AND K. DITTRICH, *Chem. Ber.*, 92 (1959) 1550–1558.
7 H. S. EL KHADEM AND M. M. MOHAMED-ALY, *J. Chem. Soc.*, (1963) 4929–4932.
8 H. S. EL KHADEM, Z. M. EL SHAFEI, AND M. M. A. ABDEL RAHMAN, *Carbohydr. Res.*, 1 (1965) 31–37.
9 H. S. EL KHADEM, M. M. A. ABDEL RAHMAN, AND M. A. SALAM, *J. Chem. Soc.*, (1968) 2411–2414.
10 H. EL KHADEM, *J. Org. Chem.*, 29 (1964) 3072–3074.
11 H. EL KHADEM, Z. M. EL SHAFEI, AND M. M. MOHAMED-ALY, *J. Org. Chem.*, 29 (1965) 1565–1567.
12 Z. M. EL SHAFEI AND E. S. H. EL ASHRY, *Carbohydr. Res.*, 3 (1966) 184–190.