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ON THE RING TRANSFORMATION OF HYDRAZINE DERIVATIVES OF L-ASCORBIC ACID INTO NITROGEN HETEROCYCLIC DERIVATIVES*

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ABSTRACT

L-*threo*-2,3-Hexodiulosono-1,4-lactone 2-(*p*-methoxyphenylhydrazone) (**1**) was condensed with arylhydrazines to give mixed bishydrazones, whose acetylation gave the corresponding di-*O*-acetyl derivatives. The hydrazone **1** undergoes elimination of one molecule of water per molecule during the acetylation, and gives 4-(2-acetoxyethylidene)-4-hydroxy-2,3-dioxobutano-1,4-lactone 2-(*p*-methoxyphenylhydrazone), which reacts with methylhydrazine, *via* a ring transformation process, to give 1-methyl-3-(1-methylpyrazolin-3-yl)-4,5-pyrazoledione 4-(*p*-methoxyphenylhydrazone). Alkali rearranged the mixed bishydrazones to 1-aryl-3-(L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(*p*-methoxyphenylhydrazones), which gave triacetyl and tribenzoyl derivatives, and, upon periodate oxidation, afforded 1-aryl-3-formyl-4,5-pyrazolediones 4-(*p*-methoxyphenylhydrazones) that gave the corresponding phenylhydrazones. The n.m.r. and mass spectra of some of these derivatives have been investigated.

INTRODUCTION

In previous papers, the synthesis of various heterocyclic derivatives in the carbohydrate series has been described[1–11]. A prerequisite for such a study is the presence of a functional group that acts as a carbonyl group in heterocyclization (such as that present in ascorbic acids used for the synthesis of flavazoles[7,12], imidazoles[13], pyrazines[14], pyrazoles[11], quinoxalines[7,12], and triazoles[15]) through its reaction with phenylhydrazine or *o*-phenylenediamine; such heterocyclization may be accompanied by ring transformation. In this report, we describe some ring transformations of L-ascorbic acid into pyrazole and pyrazoline derivatives having an electron-donating group.

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*Heterocycles from Carbohydrate Precursors. Part XII. For Part XI, see ref. 1.
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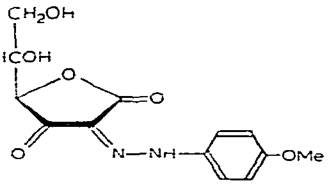
DISCUSSION

Condensation of equimolar amounts of L-*threo*-2,3-hexodiulosono-1,4-lactone and *p*-methoxyphenylhydrazine affords L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(*p*-methoxyphenylhydrazone) (**1**) which, upon acetylation, undergoes β-elimination of acetic acid from the 5,6-di-*O*-acetyl-L-*threo*-2,3-hexodiulosono-1,4-lactone 2-(*p*-methoxyphenylhydrazone) presumably formed, to give 4-(2-acetoxyethylidene)-4-hydroxy-2,3-dioxobutano-1,4-lactone 2-(*p*-methoxyphenylhydrazone) (**2**). This elimination was evidenced by the elemental analysis and the spectral data. The infrared (i.r.) spectra of **1** and **2** showed two and three bands, respectively, in the carbonyl-frequency region: one at 1660–1655 cm^{-1} (due to the carbonyl group), the second, at 1740 cm^{-1} for **1**, and at 1770 cm^{-1} for **2** (due to the lactone ring), and the third, for **2**, at 1735 cm^{-1} (due to the acetyl group). The band due to the double bond in **2** was buried within the carbonyl band. The n.m.r. spectrum of **2** showed the presence of one acetyl group as a three-proton singlet at δ 2.10, and of one hydrazone residue, as indicated by a signal for its methoxyl group as a three-proton singlet at δ 3.85. This was followed by the C-6 methylene group as a doublet of two-proton (equivalent) intensity at δ 4.88, having a coupling constant (J 7.1) of the same magnitude as that for the triplet at δ 5.87 due to H-5. The aromatic protons were centered at δ 7.28.

Reaction of **2** with 1-methylhydrazine caused it to undergo a ring-transformation process to afford a nitrogen heterocyclic derivative, namely, 1-methyl-3-(1-methylpyrazolin-3-yl)-4,5-pyrazoledione 4-(*p*-methoxyphenylhydrazone) (**3**). The i.r. spectrum of **3** showed a band at 1655 cm^{-1} (due to an OCN group), and the bands for a lactone ring and the carbonyl and acetyl groups of **2** had disappeared. The n.m.r. spectrum of **3** showed three singlets, of three-proton intensity each, at δ 3.04, 3.56, and 3.60 (due to the two methyl groups and one methoxyl group); two triplets, each of two-proton intensity, at δ 2.68 and 3.24 (due to the two adjacent methylene groups, with a coupling constant for each triplet of 3.8); a multiplet centered at δ 7.28 (due to the aromatic protons); and a singlet at δ 13.92 (due to a hydrogen-bonded, imino proton). The mass spectrum of **3** (see Scheme 1) showed a strong, molecular-ion peak at *m/e* 314, which is the base peak. This was followed by a peak at *m/e* 299 (due to the loss of a methyl group) that might lose two nitrogen atoms to give ions at *m/e* 285 and 271, respectively. The loss of MeN_2 from M^+, to give the ion 271, was confirmed by



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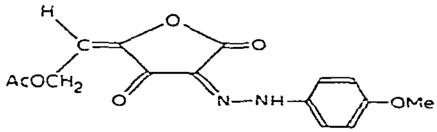

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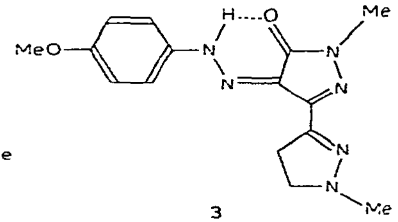

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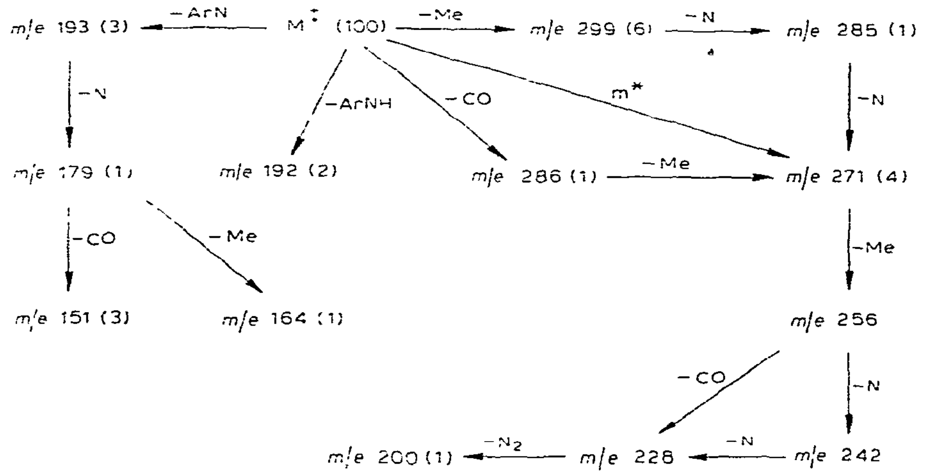
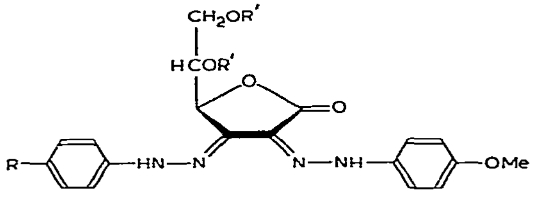
the presence of a metastable-ion peak at *m/e* 233.5 (which would be favored over the loss of CO from M^{+}, to give the ion at *m/e* 286 that, after the loss of Me, would give the ion at *m/e* 271). Further loss of methyl gave an ion at *m/e* 256 that then lost CO, to give an ion at *m/e* 228 that was followed by loss of two nitrogen atoms. Another series of ions was started by the loss of ArN or ArNH, and further loss of N and Me, or CO, giving the ions at *m/e* 193, 192, 179, 164, and 151. The ions belonging to the aromatic part appeared at *m/e* 135 ($MeOC_6H_4N_2^+$), 122 ($MeOC_6H_4NH^+$), and 108 ($MeOC_6H^+$).



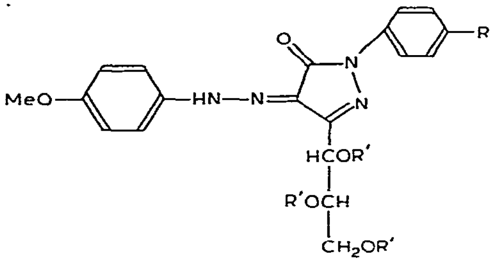
Scheme 1. The important fragments in the mass spectrum of 1-methyl-3-(1-methylpyrazolin-3-yl)-4,5-pyrazoledione 4-(*p*-methoxyphenylhydrazone) (**3**).

Condensation of **1** with phenylhydrazine and *p*-iodophenylhydrazine gave the corresponding, mixed bishydrazones **4** and **5**, respectively. Acetylation of **4** gave the di-*O*-acetyl derivative **6**. The n.m.r. spectrum of **6** showed the presence of three singlets, of three- proton intensity each, at δ 1.92, 2.00, and 3.80, due to two acetyl groups and a methoxyl group. The C-6 methylene protons appear at δ 4.4; H-4 and H-5 are buried, and appear at δ 5.72, and the aromatic protons are at δ 7.16. The presence of the two imino protons as two singlets, at δ 10.28 and 12.48, in addition to two smaller singlets at δ 10.8 and 12.00, indicated their involvement in a hydrogen-bonding and chelation process that changed with time and reached an equilibrium, as similarly observed[16] in the n.m.r. spectrum of the bis(phenylhydrazone) of the D-*erythro* isomer after 5 days.

Ring transformation of **4** (and **5**) into the corresponding pyrazolediones **7** (and **8**) was effectuated by opening of the lactone ring, and simultaneous cyclization, affording, after acidification, **7** (and **8**). The n.m.r. spectrum of **7** showed a singlet at δ 3.68 (due to the methoxyl group), two multiplets at δ 4.48 and 4.96 (due to H-6 and H-5, respectively), and a doublet at δ 5.72 (J 5.7 Hz) (due to H-1). Acetylation of **7**



4 R = R' = H
5 R = I, R' = H
6 R = H, R' = Ac

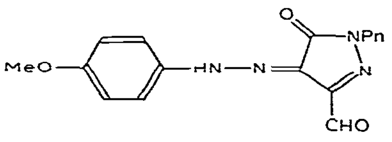


7 R = R' = H
8 R = I, R' = H
9 R = H, R' = Ac
10 R = I, R' = Ac
11 R = I, R' = Bz

and **8** gave the corresponding triacetyl derivatives **9** and **10**; their i.r. spectra showed two bands, at 1745–1740 and 1660–1650 cm^{-1} (due to OAc and OCN, respectively). The n.m.r. spectrum of 1-phenyl-(1,2,3-tri-*O*-acetyl-L-*threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(*p*-methoxyphenylhydrazone) (**8**) showed the signals of the three acetyl methyl groups at δ 2.06, 2.08, and 2.18, the last being deshielded by the heterocyclic ring. The methyl group of the methoxyl group appeared at δ 3.84. The C-3 methylene protons of the tri(acetoxy)propyl side-chain, which are nonequivalent (AB part of an ABX system) gave rise to two quartets, at δ 4.20 and 4.44, each split by a large geminal coupling ($J_{3,3'}$ 11.5 Hz) and a smaller coupling ($J_{2,3'}$ 6.0 Hz, for the first, and $J_{2,3}$ 4.2 Hz for the second). The smaller coupling-constant was attributed to the geminal proton, which is cis to H-2, and the larger coupling to the trans situation. H-2 gave rise to a multiplet of one-proton intensity at δ 5.84, split by H-3 and -1; H-1 gave rise to a doublet of one-proton intensity, at δ 6.3, split by (the trans) H-2 (J 6.2 Hz). The aromatic-proton signal occurred at δ 7.42.

Benzoylation of **8** with benzoyl chloride in pyridine afforded the corresponding tribenzoyl derivative **11**, whose i.r. spectrum showed two bands, at 1720 and 1665 cm^{-1}, due to the OBz and OCN groups, respectively.

Periodate oxidation of **7** gave 3-formyl-1-phenyl-4,5-pyrazoledione 4-(*p*-methoxyphenylhydrazone) (**12**); on reaction with phenylhydrazine, **12** afforded the corresponding hydrazone **13**.



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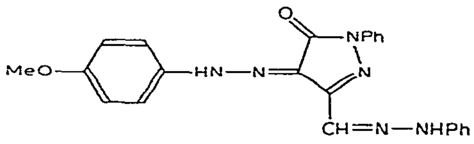

13

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler-block apparatus, and are uncorrected. I.r. spectra were recorded with a Unicam SP 200 spectrometer, and n.m.r. spectra (for solutions in pyridine-d_5 or chloroform-d) with a Jeol-100 spectrometer, with tetramethylsilane as the standard. Chemical shifts are given on the δ scale. Mass spectra were recorded with an A.E.I. MS 902 instrument. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

L-threo-*2,3-Hexodiulosono-1,4-lactone 2-*(p-*methoxyphenylhydrazone*) (**1**). — A solution of L-*threo*-2,3-hexodiulosono-1,4-lactone (1.8 g) in water (50 mL) was treated with *p*-methoxyphenylhydrazine (1.4 g) in ethanol (10 mL), and the mixture was kept overnight at room temperature, whereby a yellow, crystalline product separated out. It was filtered off, successively washed with water, ethanol, and ether, and dried (yield 60%). The product was recrystallized from ethanol, giving yellow plates, m.p. 180°; $\nu_{\max}^{\text{Nujol}}$ 3400 (OH), 1740 (COO), and 1660 cm^{-1} (CO).

Anal. Calc. for $C_{13}H_{14}N_2O_6$: C, 53.1; H, 4.8; N, 9.5. Found: C, 53.2; H, 5.1; N, 9.9.

4-(2-Acetoxyethylidene)-4-hydroxy-2,3-dioxobutano-1,4-lactone 2-(p-*methoxyphenylhydrazone*) (**2**). — A cold solution of compound **1** (0.5 g) in dry pyridine (10 mL) was treated with acetic anhydride (5 mL), and the mixture was kept for 2 h at 0° and then overnight at room temperature. The mixture was poured onto crushed ice, and the product that separated out was filtered off, washed repeatedly with water, dried (yield 70%), and recrystallized from chloroform–ethanol, giving yellow needles; m.p. 161°; $\nu_{\max}^{\text{Nujol}}$ 1770 (COO), 1735 (OAc), and 1655 cm^{-1} (CO and C=C); n.m.r. data ($CDCl_3$): δ 2.10 (s, 3, COMe), 3.85 (s, 3, OMe), 4.88 (d, 2, CH_2, J 7.1), 5.87 (t, 1, HC=), and 7.28 (m, Ar).

Anal. Calc. for $C_{15}H_{14}N_2O_6$: C, 56.6; H, 4.4; N, 8.8. Found: C, 56.2; H, 4.5; N, 9.1.

1-Methyl-3-(1-methylpyrazolin-3-yl)-4,5-pyrazoledione 4-(p-*methoxyphenylhydrazone*) (**3**). — A solution of compound **2** (0.6 g) in ethanol (0.5 mL) was treated with methylhydrazine (0.5 mL), and boiled for 10 min. The mixture was cooled, and the product that separated was filtered off, washed with a little ethanol, and dried (yield 80%). The product was recrystallized from ethanol, giving orange needles, m.p. 225°; $\nu_{\max}^{\text{Nujol}}$ 1655 cm^{-1} (OCN); n.m.r. data (C_5D_5N): δ 2.68 (t, 2, CH_2, J 3.8), 3.04 (s, 3, NMe), 3.24 (t, 2, CH_2), 3.56 (s, 3, NMe), 3.60 (s, 3, OMe), and 7.28 (m, 4, Ar).

Anal. Calc. for $C_{15}H_{18}N_6O_2$: C, 57.3; H, 5.8; N, 26.7. Found: C, 57.1; H, 6.2; N, 27.1.

L-threo-*2,3-Hexodiulosono-1,4-lactone 2-*(p-*methoxyphenylhydrazone*) *3-*(*phenylhydrazone*) (**4**). — A solution of **1** (0.01 mole) in ethanol (20 mL) was treated with phenylhydrazine (0.01 mole) and few drops of acetic acid. The mixture was heated for 10 min, diluted with water, and cooled, whereby the red bis(hydrazone) separated out. It was recrystallized from ethanol, m.p. 193–195°; ν_{max}^{Nujol} 1735 (sh) and 1725 cm^{-1} (COO).

Anal. Calc. for $C_{19}H_{20}N_4O_5$: C, 59.4; H, 5.2; N, 14.6. Found: C, 59.4; H, 5.4; N, 14.9.

L-threo-*2,3-Hexodiulosono-1,4-lactone 3-*(p-*iodophenylhydrazone*) *2-*(p-*methoxyphenylhydrazone*) (**5**). — This was prepared as for **4**: m.p. 221–222°; ν_{max}^{Nujol} 1760 and 1730 cm^{-1} (COO).

Anal. Calc. for $C_{19}H_{19}IN_4O_5$: C, 44.7; H, 3.8; N, 11.0. Found: C, 44.6; H, 4.0; N, 11.2.

*5,6-Di-*O*-acetyl-*L-threo-*2,3-hexodiulosono-1,4-lactone 2-*(p-*methoxyphenyl hydrazone*) *3-(phenylhydrazone*) (**6**). — A suspension of **4** (0.1 g) in pyridine (5 mL) was treated with acetic anhydride (5 mL), and kept overnight at room temperature. The mixture was poured onto crushed ice, and the solid was filtered off, washed repeatedly with water, and dried (yield 70%). It was recrystallized from chloroform–ethanol, giving orange needles, m.p. 185°; ν_{max}^{Nujol} 1740 cm^{-1} (OAc); n.m.r. data (Me_2SO-d_6): δ 1.92 (s, 3, COMe), 2.08 (s, 3, COMe), 3.80 (s, 3, OMe), 4.4 (m, 2, H-6,6′), 5.72 (m, 2, H-4,5), and 7.16 (m, 9, Ar).

Anal. Calc. for $C_{23}H_{24}N_4O_7$: C, 59.0; H, 5.2; N, 12.0. Found: C, 59.3; H, 5.0; N, 12.3.

3-(L-threo-*Glycerol-1-yl*)*-1-phenyl-4,5-pyrazoledione 4-*(p-*methoxyphenylhydrazone*) (**7**). — A suspension of **4** (1 g) in water (50 mL) was heated with 2M sodium hydroxide (25 mL) for 5 min at 70–80°, whereby the osazone completely dissolved. The pH was then brought to 7 with acetic acid, and the product was filtered off, washed several times with water, and recrystallized from ethanol, giving orange needles, m.p. 200–203°; ν_{max}^{Nujol} 1660 cm^{-1} (OCN); n.m.r. data (C_5D_5N): δ 3.68 (s, 3, OMe), 4.48 (m, 2, H-3,3′), 4.96 (m, 1, H-2), 5.72 (d, 1, H-1, J 5.7), and 7.6 (m, 9, Ar).

Anal. Calc. for $C_{19}H_{20}N_4O_5$: C, 59.4; H, 5.2; N, 14.6. Found: C, 59.3; H, 5.1; N, 14.8.

3-(L-threo-*Glycerol-1-yl*)*-1-*p-*iodophenyl-4,5-pyrazoledione 4-*(p-*methoxyphenylhydrazone*) (**8**). — This was prepared similarly to **7**; m.p. 234–235°; ν_{max}^{Nujol} 1660 cm^{-1} (OCN).

Anal. Calc. for $C_{19}H_{19}IN_4O_5$: C, 44.7; H, 3.8; N, 11.0. Found: C, 45.0; H, 4.1; N, 11.1.

1-Phenyl-3-(*1,2,3-tri-*O*-acetyl-*L-threo-*glycerol-1-yl*)*-4,5-pyrazoledione 4-*(p-*methoxyphenylhydrazone*) (**9**). — A solution of **7** (0.3 g) in dry pyridine (10 mL) was treated with acetic anhydride (5 mL), and kept overnight at room temperature. The mixture was poured onto crushed ice, and the product was filtered off, washed repeatedly with water, and dried (yield 80%). It was recrystallized from chloroform–ethanol, giving yellow-orange needles, m.p. 182–183°; ν_{max}^{Nujol} 1740 (OAc) and 1650 cm^{-1} (OCN); n.m.r. data ($CDCl_3$): δ 2.06 (s, 3, COMe), 2.08 (s, 3, COMe), 2.18 (s, 3, COMe), 3.84 (s, 3, OMe), 4.32 (2 q, 2, H-3,3′, $J_{3,3'}$ 11.5, $J_{3,2}$ 4.2, $J_{3',2}$ 6.0 Hz), 5.84 (m, 1, H-2), and 6.3 (d, 1, H-1, $J_{1,2}$ 6.2 Hz), and 7.42 (m, 9, Ar).

Anal. Calc. for $C_{25}H_{26}N_4O_8$: C, 58.8; H, 5.1; N, 11.0. Found: C, 58.4; H, 5.2; N, 11.2.

*1-*p*-Iodophenyl-3-(1,2,3-tri-*O*-acetyl-*L-threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(*p*-methoxyphenylhydrazone)* (**10**). — This was prepared similarly to **9**; m.p. 144–145°; ν_{max}^{Nujol} 1740 (OAc) and 1660 cm^{-1} (OCN).

Anal. Calc. for $C_{25}H_{25}IN_4O_8$: C, 47.2; H, 4.0; N, 8.8. Found: C, 47.5; H, 4.2; N, 9.1.

*1-*p*-Iodophenyl-3-(1,2,3-tri-*O*-benzoyl-*L-threo*-glycerol-1-yl)-4,5-pyrazoledione 4-(*p*-methoxyphenylhydrazone)* (**11**). — A solution of **8** (0.1 g) in dry pyridine (5 mL) was treated with benzoyl chloride (0.5 mL), and kept overnight at room temperature. The mixture was poured onto crushed ice, and the product was filtered off, washed repeatedly with water, and dried (yield 70%). It was recrystallized from chloroform–ethanol, giving orange needles, m.p. 190–191°; ν_{max}^{Nujol} 1720 (OBz) and 1665 cm^{-1} (OCN).

Anal. Calc. for $C_{40}H_{31}IN_4O_8$: C, 58.4; H, 3.8; N, 6.8. Found: C, 58.8; H, 3.8; N, 6.9.

*3-Formyl-1-phenyl-4,5-pyrazoledione 4-(*p*-methoxyphenylhydrazone)* (**12**). — A solution of **7** (1 g) in ethanol (30 mL) was treated with a solution of periodic acid (1 g) in water (10 mL), and kept for 1 h at room temperature. The mixture was diluted with water, and the product that separated was filtered off, successively washed with water, ethanol, and ether, and dried (yield 70%). It was recrystallized from ethanol, giving yellow-orange needles, m.p. 160–162°; ν_{max}^{Nujol} 1695 (CHO) and 1660 cm^{-1} (OCN).

Anal. Calc. for $C_{17}H_{14}N_4O_3$: C, 63.4; H, 4.4; N, 17.4. Found: C, 63.2; H, 4.5; N, 17.3.

*3-Phenylhydrazone of 3-formyl-1-phenyl-4,5-pyrazoledione 4-(*p*-methoxyphenylhydrazone)* (**13**). — A solution of **12** (0.1 g) in ethanol (10 mL) was treated with phenylhydrazine (0.1 mL), and the mixture was boiled under reflux for 10 min. The product that separated was filtered off, successively washed with water and ethanol, and dried (yield 75%). It was recrystallized from ethanol, giving red needles, m.p. 196–198°; ν_{max}^{Nujol} 1675 cm^{-1} (OCN).

Anal. Calc. for $C_{23}H_{20}N_6O_2$: C, 67.0; H, 4.9; N, 20.4. Found: C, 67.2; H, 4.8; N, 20.4.

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