Studies With Quinolines: New Synthetic Routes to 4*H*,5*H*,6*H*,9*H*-Benzo[*ij*]pyrano[2,3-*b*]quinolizine-8-one, 4*H*-Pyrano[2,3-*b*]pyridine, 2*H*-Pyran-2-one and Pyranopyridoquinoline Derivatives

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Several new benzo[*ij*]pyrano[2,3-*b*]quinolizine-8-ones **5** and 4*H*-pyrano[2,3-*b*]pyridine **8** derivatives were synthesized from 4-hydroxyquinolines **1**. Reacting 3-acetyl-4-hydroxy-1-phenyl-1*H*-quinoline-2-one with dimethylformamide dimethylacetal afforded 3-(3-Dimethylamino-acryloyl)-4-hydroxy-1-phenyl-1*H*-quinolin-2-one **9**. This reacted with hippuric acid and diethyl 3-oxoglutarate to give 2*H*-pyran-2-one **13** and pyranopyridoquinoline **17** respectively.

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Introduction.

4-Hydroxy-1*H*-quinolin-2-ones are versatile reagents and their utility in synthesis of different heterocycles has recently received considerable interest [1-6]. Also, they have occupied a unique place in medicinal and biological chemistry due to their diverse pharmacological displays as antitumor [7], antimicrobial [8], antidepressant [9] and antiseptic agents [10]. They are also useful intermediates in the manufacture of dyestuffs [11]. Although a large number of substituted derivatives of the above mentioned biologically interesting quinolines have been prepared, no simple general route for derivatives of these ring systems is available.

Enaminones are an interesting class of compounds that are versatile and readily available intermediates and play an important role as building blocks in the synthesis of many aromatic and heteroaromatic systems [12-16]. In spite of the many literature reports on enaminones, little attention has been paid to the corresponding enaminones containing the quinolinyl moiety. In continuation of our studies in exploring the utilization of substituted quinolines as versatile precursors for synthesis of a variety of heteroaromatics like 3-substituted quinolines and pyranoquinolines, we report here new accesses to 3-subtituted quinolines and pyrano[3,2-*c*]quinoline derivatives.

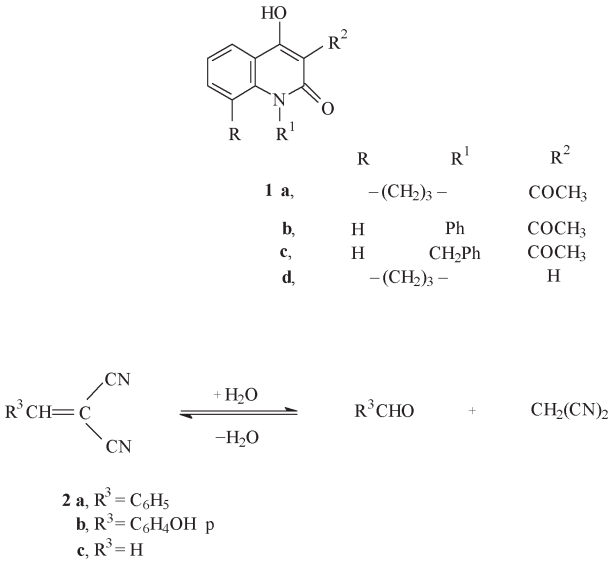

Figure 1

Results and Discussion.

It has been found that, 1-hydroxy-2-acetyl-6,7-dihydro-5*H*-benzo[*i,j*]quinolin-3-one (**1a**) reacted readily with arylidenemalononitriles (**2a,b**) in ethanol with a piperidine catalyst affords 9-aryl-11-amino-10-cyano-4*H*,5*H*,6*H*,9*H*-benzo[*ij*]pyrano[2,3-*b*]quinolizin-8-ones (**5a,b**) Structures **5a,b** were established on the basis of their ^{1}H-nmr spectra which displayed 4*H*-pyran protons at $\delta \approx 4.5$ ppm. Formation of **5a,b** from **1a** and **2a,b** is assumed to proceed *via* initial addition of quinolizinyl C-2 in **1a** to the π-deficient double bond in **2** to give the adducts **3**, which then converted into the intermediates **4** *via* deacetylation as has been previously reported [6]. The intermediates **4** were cyclized to yield the final isolable products **5**. It is of value to note that quinolizinyl C-2 in **1a** is more acidic than its acetyl group. Moreover, the steric effect in the adducts **3** facilitate the deacetylation process. This mechanism is supported further from the finding that **5a,b** are formed from 1-hydroxy-6,7-dihydro-5*H*-benzo[*i,j*]quinolin-3-one (**1d**) with the same reagents.

Also, 11-amino-10-cyano-4*H*,5*H*,6*H*,9*H*-benzo[*ij*]-pyrano[2,3-*b*]quinolizin-8-one (**5c**) was prepared *via* the reaction of 2-acetyl-1-hydroxy-6,7-dihydro-5*H*-pyrido-[3,2,1-*ij*]quinolin-3-one (**1a**) with methylenemalononitrile (**2c**), prepared *in situ* from a mixture of formaldehyde and malononitrile. The structure of **5c** was assigned based on elemental composition and spectral data and is consistent with the product expected from the reaction of **1c** with methylenemalononitrile **2c** (Scheme 1).

In contrast to the behaviour of compound **1a** towards arylidenemalononitriles **2**, 3-acetyl-4-hydroxy-1-substituted-2(1*H*)-quinolones (**1b,c**) reacted with arylidenemalononi-

triles **2a,b** in ethanol/piperidine in a molar ratio (1:1) or (1:2) to yield pyrano[2,3-*b*]pyridine derivatives **8a-c**. Elemental analysis and spectral data are in full agreement with the proposed structures **8** (*cf*. Experimental). Compounds **8** are likely formed *via* Michael type addition of the enolate ion of the acetyl function in **1b,c** to the activated double bond in **2** to give the acyclic adducts **6**, which cyclized into the intermediates **7**. The intermediates **7** then add one molecule of malononitrile, which exists in equilibrium with **2** especially under basic conditions [6] to afford compounds **8**.

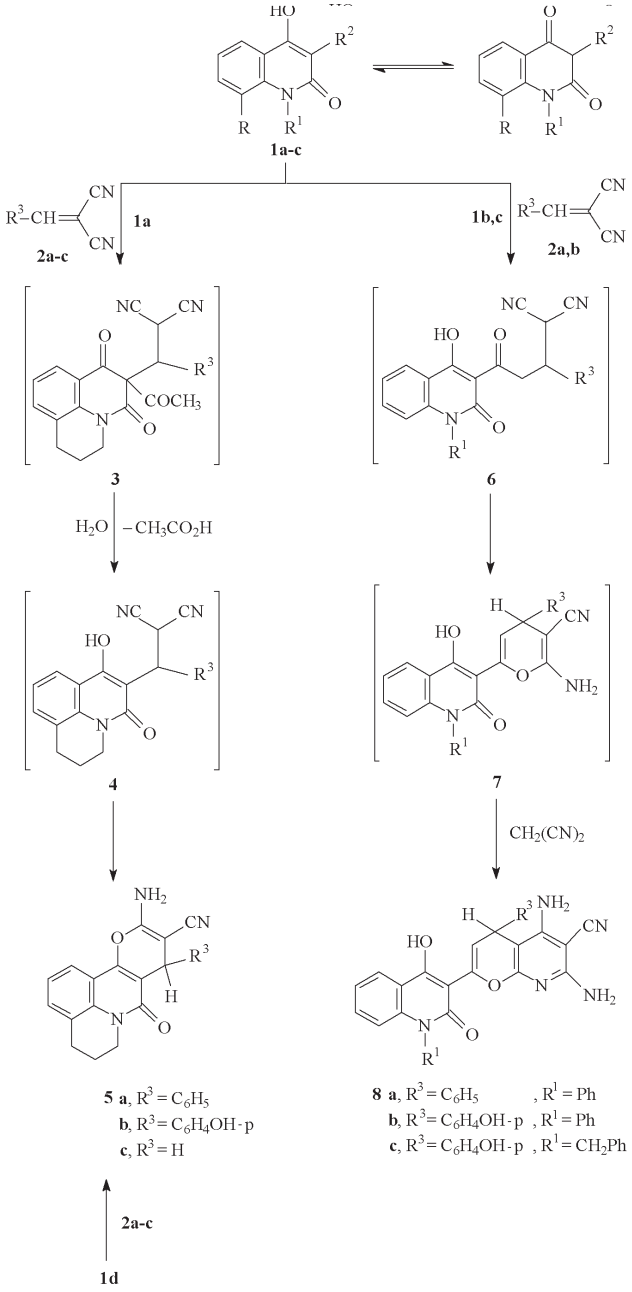

Figure 2

In conjunction of our investigations on the synthesis of quinoline derivatives of potential interest using *N,N*-dimethylformamide dimethylacetal (DMFDMA) as versatile starting material, we have studied the condensation of 3-acetyl-4-hydroxy-1-phenyl-2(1*H*)-quinolone (**1b**) with *N,N*-dimethylformamide dimethylacetal followed by reaction with different reagents. Thus, treatment of 3-acetyl-4-hydroxy-1-phenyl-2(1*H*)-quinolone (**1b**) with *N,N*-dimethylformamide dimethylacetal in dry xylene/ dimethylformamide mixture (1:1) at reflux temperature afforded a product with molecular formula $C_{20}H_{18}N_2O_3$ (M^+ = 334 m/z), which is consistent with 1-(4-hydroxy-2-one-1-pheny-qninolin-3-yl)-3-dimethylaminoprop-2-ene-1-one (**9**) as the reaction product.

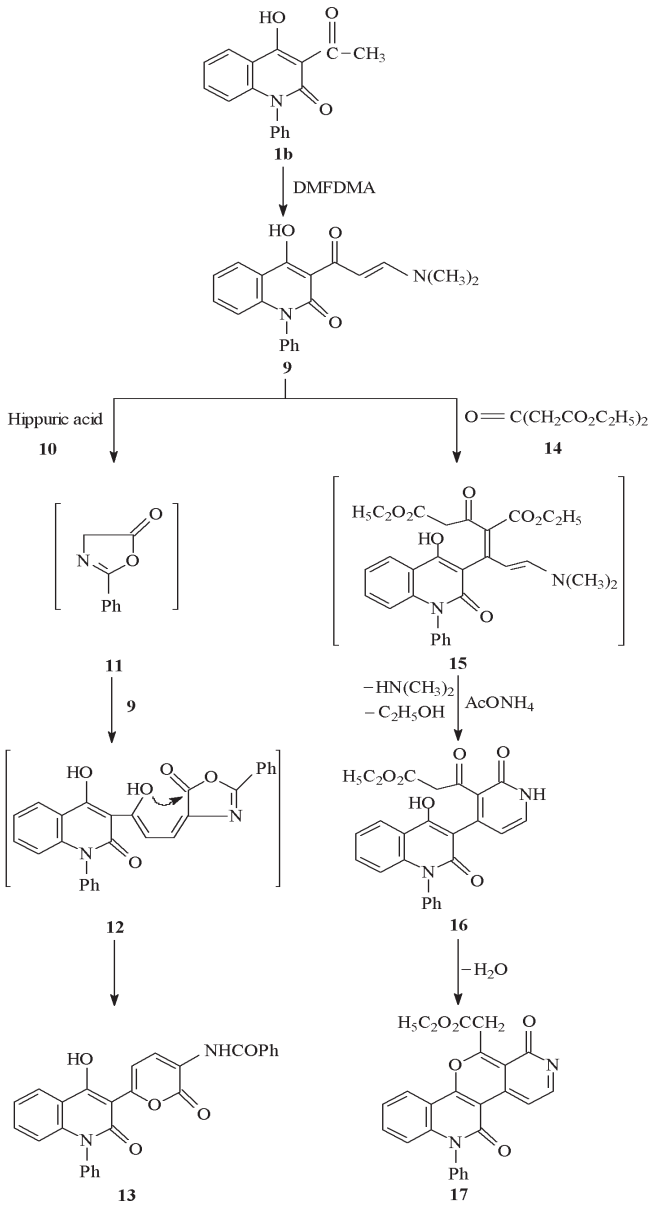

Figure 3

Reacting compound **9** with hippuric acid **10** in acetic anhydride afforded *N*-[6-(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)-2-oxo-2*H*-pyran-3-yl]-benzamide (**13**). These were assumed to be formed *via* initial cyclization of hippuric acid **10** into oxazolone **11** which then adds to the activated double bond system of the enaminone **9** yielding **12** followed by further rearrangement of **12** to give **13**. Similar sequence has been recently reported for the reaction of enaminones with hippuric acid [14].

The enaminone **9** was also reacted with diethyl acetonedicarboxylate (**14**) in acetic acid with ammonium acetate catalyst to give a product with molecular formula $C_{25}H_{18}N_2O_5$ (M^+ = 426). The IR spectrum of the reaction product showed absorption bands at ν = 1739 cm^{-1} (CO ester), 1713 cm^{-1} (CO pyridine), 1637 cm^{-1} (CO amide). Consequently, 2-ethoxycarbonylmethyl-3,7,8-trihydro-8-phenyl-pyrano[3,4-b]pyrido[4,3-b]quinoline-3,7-dione (**17**) was assigned as a reaction product.

Compound **17** is thought to be formed via condensation of the active methylene in **14** with the carbonyl function in **9** with water elimination forming the intermediate **15**. The later was cyclized in presence of ammonium acetate via elimination of molecule of and water to afford the final product **17**.

EXPERIMINTAL

All melting points are uncorrected. IR spectra were recorded for KBr disks on a Shimadzu IR-740 spectrometer. ^{1}H-nmr spectra were obtained on a Bruker AC-80 spectrometer with DMSO-d_6 as solvent and TMS as an internal standard and chemical shifts are expressed as δ ppm. Mass spectra were measured on GC-MSINCOS XL Finnigan MAT. Elemental analyses were performed on LECO CHNS-932.

Synthesis of Quinolones **5a-c**.

Method A.

A mixture of 1-hydroxy-2-acetyl-6,7-dihydro-5*H*-benzo[*ij*]-quinolin-3-one (**1a**) (0.01 mol) and (0.01 mol) of **2a-c** in ethanol (50 ml) containing a few drops of piperidine were refluxed for half an hour, then left to cool. The obtained precipitate was collected by filtration and recrystallized from ethanol/DMF and then identified as **5a-c**.

Method B.

Compounds **5a-c** were also prepared from 1-hydroxy-6,7-dihydro-5*H*-benzo[*ij*]quinolin-3-one (**1d)** (0.01 mol) and (0.01 mol) **2a-c** utilizing the above reaction conditions.

11-Amino-10-cyano-9-phenyl-4*H*,5*H*,6*H*,9*H*-benzo[*ij*]pyrano-[2,3-*b*]quinolizin-8-one (**5a**).

Compound **5a** was obtained as colorless crystals in 60% yield m.p. > 300 °C; ir (KBr): ν 3393, 3326 (NH_2), 2198 (CN), 1675 (CO) cm^{-1}; ^{1}H-nmr (DMSO): δ 1.95 (m, 2H, CH_2), 2.5 (t, J = 6Hz, 2H, Ar-CH_2), 3.95 (t, J = 6Hz, 2H, N-CH_2), 4.54 (s, 1H, pyran H-4), 7.16-7.45 (m, 9H, 7H, Ar-H and 2H, NH_2) 7.9 (d, J = 8Hz, 1H, quinolizine H-9); ms: 355 (M^+).

Anal. Calcd. For $C_{22}H_{17}N_3O_2$ (355.4): C, 74.35; H, 4.82; N, 11.82. Found: C, 74.41; H, 4.76; N, 11.90.

11-Amino-10-cyano-9-(4-hydroxyphenyl)-4*H*,5*H*,6*H*,9*H*-benzo-[*ij*]pyrano[2,3-*b*]quinolizin-8-one (**5b**).

Compound **5b** was obtained as yellow crystals in 65% yield m.p. 290 °C; ir (KBr): ν 3444, 3290 (NH_2), 2188 (CN), 1670 (CO) cm^{-1}; ^{1}H-nmr (DMSO): δ 1.94 (m, 2H, CH_2), 2.94 (t, J = 6Hz, 2H, Ar-CH_2), 3.94 (t, J = 6Hz, 2H, N-CH_2), 4.4 (s, 1H, pyran H-4), 6.6 (d, J = 9Hz, 2H, Ar-H), 6.85 (d, J = 9Hz, 2H, Ar-H), 7.19 (s, 2H, NH_2), 7.42 (t, J = 8Hz, 1H, quinolizine H-9), 7.42 (d, J = 8Hz, 1H, quinolizine H-8), 7.83 (d, J = 8Hz, 1H, quinolizine H-10) 9.72 (s, 1H, OH); ms: 371 (M^+).

Anal. Calcd. For $C_{22}H_{17}N_3O_3$ (371.4): C, 71.15; H, 4.61; N, 11.31. Found: C, 71.31; H, 4.57; N, 11.23.

11-Amino-10-cyano-4*H*,5*H*,6*H*,9*H*-benzo[*ij*]pyrano[2,3-*b*]-quinolizin-8-one (**5c**).

Compound **5c** was obtained as colorless crystals in 70% yield m.p. > 300 °C; ir (KBr): ν 3323, 3300 (NH_2), 2192 (CN), 1677 (CO) cm^{-1}; ^{1}H-nmr (DMSO): δ 1.96 (m, 2H, CH_2), 2.91 (t, J = 6Hz, 2H, Ar-CH_2), 3.34 (s, 2H, pyran H-4), 4.02 (t, J = 6Hz, 2H, N-CH_2), 7.11 (s, 2H, NH_2), 7.21 (t, J = 7Hz, 1H, quinolizine H-9), 7.41 (d, J = 7Hz, 1H, quinolizine H-8), 7.7 (d, J = 7Hz, 1H, quinolizine H-10); ms: 279 (M^+).

Anal. Calcd. for $C_{16}H_{13}N_3O_2$ (279.3): C, 68.81; H, 4.69; N, 15.05. Found: C, 68.76; H, 4.73; N, 15.21.

Preparation of 5,7-Diamino-4-aryl-2-(1-aryl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-pyrano[2,3-*b*]pyridine-6-carbonitriles (**8a-c**).

To a solution of 3-acetyl-4-hydroxy-1-substituted-2(1*H*)-quinolones (**1b,c**) (0.01 mol) in ethanol containing few drops of piperidine, (0.01 mol) of **2a,b** were added. The reaction mixture was refluxed for one hour, and then left to cool at room temperature. The solid product that formed was collected by filtration and recrystallized from ethanol/1,4-dioxane to give **8a-c**.

5,7-Diamino-2-(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)-4-phenyl-4*H*-pyrano[2,3-*b*]pyridine-6-carbonitrile (**8a**).

Compound **8a** was obtained as colorless crystals in 75% yield m.p. > 300 °C; ir (KBr): ν 3450, 3380, 3200 (NH_2, OH), 2200 (CN), 1680 (CO) cm^{-1}; ^{1}H-nmr (DMSO): δ 4.53 (s, 1H, pyran H-4), 6.6 (d, J = 8.5Hz, 1H, Ar-H), 7.1-7.6 (m, 15H, 13H, Ar-H and 4H, $2NH_2$), 8.1 (d, J = 8.5 Hz, 1H, quinoline H-8); ms: 499 (M^+).

Anal. Calcd. for $C_{30}H_{21}N_5O_3$ (499.53): C, 72.13; H, 4.24; N, 14.02. Found: C, 72.24; H, 4.16; N, 14.13.

5,7-Diamino-2-(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)-4-(4-hydroxyphenyl)-4*H*-pyrano[2,3-*b*]pyridine-6-carbonitrile (**8b**).

Compound **8b** was obtained as yellow crystals in 70% yield m.p. > 300 °C; ir (KBr): ν 3460, 3338, 3124 (NH_2, OH), 2210 (CN), 1636 (CO) cm^{-1}; ^{1}H-nmr (DMSO): δ 4.5 (s, 1H, pyran H-4), 6.51(d, J = 8.5Hz, quinoline H-7), 6.63 (d, J = 8.5Hz, 2H, Ar-H), 7.2 (d, J = 8.5 Hz, 2H, Ar-H), 7.4-7.8 (m, 13H, 9H, Ar-H and 4H, $2NH_2$), 8.2 (d, J = 8.5 Hz, 1H, Quinoline H-8), 9.5 (s, 1H, OH); ms: 515 (M^+).

Anal. Calcd. for $C_{30}H_{21}N_5O_4$ (515.53): C, 69.90; H, 4.11; N, 13.59. Found: C, 69.89; H, 4.22; N, 13.61.

5,7-Diamino-2-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4-(4-hydroxyphenyl)-4*H*-pyrano[2,3-*b*]pyridine-6-carbonitrile (**8c**).

Compound **8c** was obtained as yellow crystals in 65% yield m.p. 260-262 °C; ir (KBr): ν 3464, 3310, 3216 (NH_2, OH), 2200 (CN), 1680 (CO) cm^{-1}; ^{1}H-nmr (DMSO): δ = 4.6 (s, 1H, pyran H-4), 5.41(s, 2H, CH_2), 6.67 (d, J = 8.5Hz, quinoline H-7), 7.2 (d, J = 8.5 Hz, 2H, ArH), 7.35 (m, 12H, 8H, Ar-H and 4H, $2NH_2$), 8.1 (d, J = 8.5 Hz, 1H, quinoline H-8), 9.3 (s, 1H, OH), 10.2 (s, 1H, OH); ms: 529 (M^+).

Anal. Calcd. for $C_{31}H_{23}N_5O_4$ (529.56): C, 70.31; H, 4.38; N, 13.23. Found: C, 70.43; H, 4.33; N, 13.44.

3-(3-Dimethylamino-acryloyl)-4-hydroxy-1-phenyl-1*H*-quinolin-2-one (**9**).

Dimethylformamide dimethylacetal (0.01 mol) was added to 3-acetyl-4-hydroxy-1-phenyl-2(1*H*)-quinolone (**1b**) (0.01 mol) in dry xylene (50 ml) and the reaction mixture was refluxed for 6 hours. Removal of the solvent under reduced pressure yielded the crude product, which was recrystallized from DMF to give **9** as orange crystals in 70% yield, m.p. 270-272 °C; ir (KBr): ν 3450, 3137 (OH), 1680 (CO), 1660 (CO), 1604 (C=C) cm^{-1}; ms: 334 (M^+).

Anal. Calcd. for $C_{20}H_{18}N_2O_3$ (334.38): C, 71.84; H, 5.43; N, 8.38. Found: C, 71.78; H, 5.51; N, 8.39.

N-[6-(4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)-2-oxo-2*H*-pyran-3-yl]-benzamide (**13**).

A solution of **9** (0.01 mol) and the appropriate amount of hippuric acid **10** (0.01 mol) in acetic anhydride (50 ml), was refluxed for 3 hours, then left to cool. The deposited solid was isolated by filtration and recrystallized from ethanol/DMF to give **13** as red crystals in 65% yield, m.p. 244-246 °C; ir (KBr): ν 3508, 3406 (OH, NH), 1785 (CO pyrone), 1702 (CO), 1668 (CO amide) cm^{-1}; ms: 450 (M^+).

Anal. Calcd. for $C_{27}H_{18}N_2O_5$ (450.45): C, 71.99; H, 4.03; N, 6.22. Found: C, 71.89; H, 4.13; N, 6.34.

(1*H*,5*H*,6*H*-1,5-Dioxo-6-phenylpyrido[4',3':4,5]pyrano[3,2-*c*]-quinolin-12-yl)-acetic Acid Ethyl Ester (**17**).

Compound **9** (0.01 mol) and (0.01 mol) of diethyl acetonedicarboxylate (**14**) and (0.01 mol) of ammomium acetate in glacial acetic acid (30 ml) were refluxed for one hour then left to cool to room temperature. The material that precipitated upon cooling was isolated by filtration and recrystallized from ethanol to give **17** as yellow crystals in 60% yield, m.p. 200-202 °C; ir (KBr): ν 1739 (CO ester), 1713 (CO), 1637 (CO) cm^{-1}; ms : 426 (M^+).

Anal. Calcd. for $C_{25}H_{18}N_2O_5$ (426.43): C, 70.42; H, 4.25; N, 6.57; Found: C, 70.51; H, 4.22; N, 6.63.

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