

A Study of the Catalytic Reductive Products of 2,3-Dihydro-6-methoxy-3-(6-nitroveratrylidene)-4*H*-benzopyran-4-one. Part II.

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Although the previously reported (1,2) chemical reduction of 2,3-dihydro-3-(6-nitroveratrylidene)-4*H*-benzopyran-4-one with stannous chloride occurred with cyclization to the 6*H*-[1]-benzopyrano[4,3-*b*]quinoline ring system, the present study of the catalytic (palladium/carbon) reduction of 2,3-dihydro-6-methoxy-3-(6-nitroveratrylidene)-4*H*-benzopyran-4-one (**1**) (**3**) has indicated that other products in addition to the expected benzopyranoquinoline (**3**) may be isolated, depending upon the conditions of the reduction. The products of the reduction of **1**, isolated and structurally determined, include 2,9,10-trimethoxy-6*H*-[1]benzopyrano[4,3-*b*]quinoline (**3**), 2,9,10-trimethoxy-6a,7,12,12a-tetrahydro-6*H*-[1]benzopyrano[4,3-*b*]quinoline (**2**), the *N*-oxide of **3** (**6**), and 6-hydroxy-2,9,10-trimethoxy-6*H*-[1]benzopyrano[4,3-*b*]quinoline (**8**).

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Discussion

The 6*H*-[1]benzopyrano[4,3-*b*]quinoline ring system was previously synthesized through a), the direct condensation of a 2,3-dihydro-4*H*-benzopyran-4-one with an *o*-aminobenzaldehyde(1,4,5) and b), the condensation of 4*H*-benzopyran-4-one and *o*-nitrobenzaldehyde with subsequent chemical reduction (1,2). The present paper covers the isolation and structural determination of the products of the catalytic (palladium/carbon) reductive ring closure of 2,3-dihydro-6-methoxy-3-(6-nitroveratry-

lidene)-4*H*-benzopyran-4-one (**1**) (**3**).

The reductive ring closure of (**1**) was explored in detail (Scheme 1). Compound **1** was initially subjected to catalytic (palladium/carbon) hydrogenation at 35-45° until the absorption of hydrogen ceased at 5 moles per mole of **1**. Two compounds were isolated from the reaction mixture, namely 2,9,10-trimethoxy-6a,7,12,12a-tetrahydro-6*H*-[1]benzopyrano[4,3-*b*]quinoline (**2**) (48% average yield) and 2,9,10-trimethoxy-6*H*-[1]benzopyrano[4,3-*b*]quinoline (**3**) (17% average yield).

Scheme 1

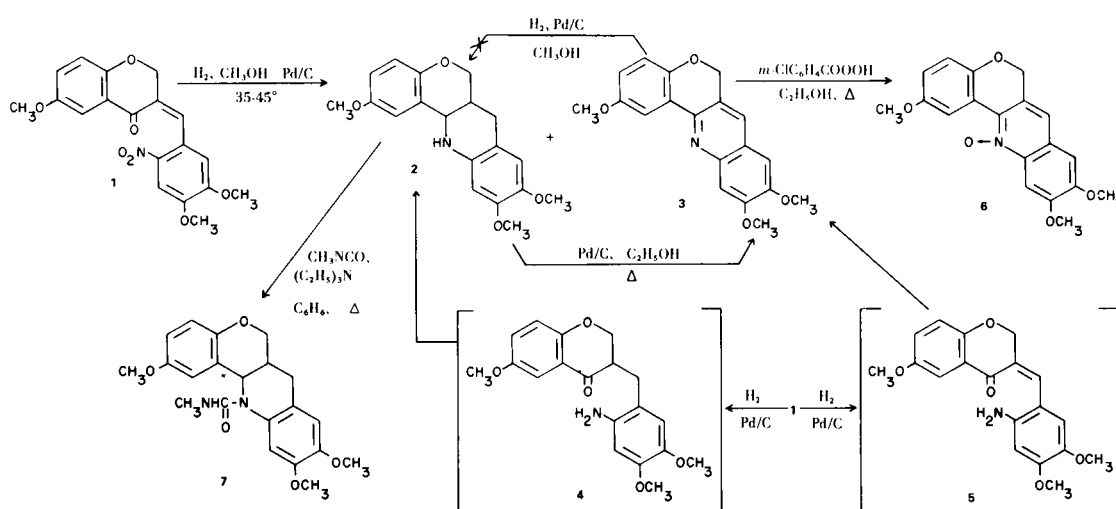
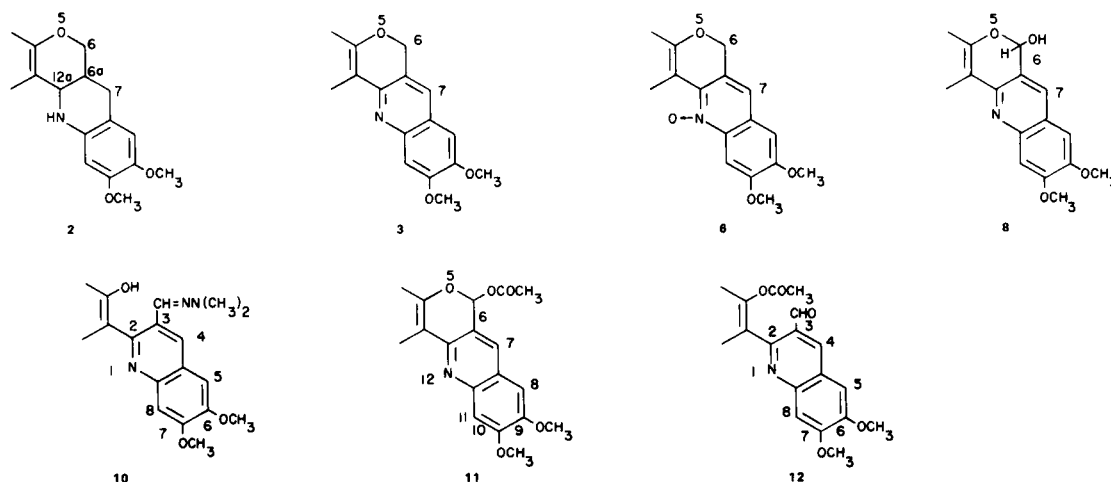


Figure 1



Although **2** was readily aromatized to **3** with palladium/carbon in refluxing ethanol, conversely **3** could not be catalytically reduced to **2** under similar conditions. Therefore, **3** was probably not an intermediate in the original formation of **2**.

Thus the probable precursor to **2** is 3-(6-aminoveratryl)-2,3-dihydro-6-methoxy-4*H*-benzopyran-4-one (**4**), and the probable precursor to **3** is 3-(6-aminoveratrylidene)-2,3-dihydro-6-methoxy-4*H*-benzopyran-4-one (**5**) (see Scheme 1). Neither **4** nor **5** has been isolated.

When the catalytic (palladium/carbon) reduction of **1** was run in the presence of methanolic hydrochloric acid, a mixture of **3** and the *N*-oxide (**6**) of **3** was obtained (85% yield) in a ratio of 1:2 (see Experimental). An authentic sample of **6** was prepared through the oxidation of **3** with *m*-chloroperbenzoic acid. The observation that **6** was generated only in the presence of acid was rather analogous to the catalytic reductive ring closure of *o*-nitro-*N*-substituted anilides to give *o*-amino-*N*-substituted anilides in neutral medium, and to give primarily 1-substituted benzimidazole *N*-oxides in acid medium (**6**).

Structural Determination

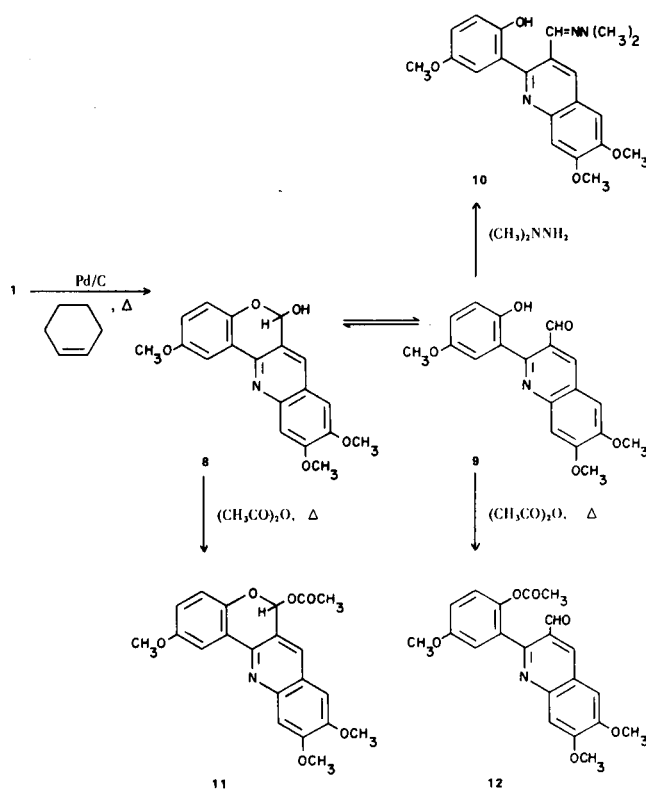
The 2,9,10-trimethoxy-6*H*-[1]benzopyrano[4,3-*b*]quinoline structure **3** is supported by physical chemical data (see Experimental) and the direct oxidation of **3** to its *N*-oxide (**6**) as described. The nmr spectrum of **3** exhibited a singlet at $\delta = 5.30$ (6-CH₂) and a triplet centered at $\delta = 7.84$ (heteromatic 7-CH), split by the allylic methylene (6-CH₂) (see Figure 1). The *N*-oxide (**6**) has the same nmr pattern as that of **3**, with the triplet peaks centered at $\delta = 9.38$ (heteromatic 7-CH) and farther downfield.

The tetrahydropyranoquinoline structure (**2**) is supported by physical chemical data, and the formation of its 12-carboxamide derivative (**7**). Significant infrared

absorption for **2** occurred at 2.96μ (NH). The nmr spectrum of **2** included multiplets at $\delta = 1.8-2.9$ (6a-CH, 7-CH₂), broad singlet at $\delta = 3.65$ (NH, exchanged with deuterium oxide), and multiplets at $\delta = 3.9-4.5$ (6-CH₂, 12a-CH).

In an attempt to isolate the postulated intermediate (**5**) of the catalytic reductive ring closure of **1** to **3** compound **1** was reduced with the mild reagent palladium/carbon-cyclohexene. Although compound **3** and the *N*-oxide (**6**)

Scheme 2



were both identified as products of the reduction (see Experimental), a third product isomeric to that of **6** was also isolated in significant yield. The isomeric product exhibited an nmr spectrum very similar to that of **6**, except that the heteromatic proton ($\delta = 9.02$, 7-CH) appeared split as a doublet (presumably by a single proton at 6-CH) instead of the observed triplets for the heteromatic proton (7-CH) in the cases of the two "model" compounds **3** and **6** (see Figure 1). Furthermore, for the isomer the (6-CH) doublet appeared much further downfield ($\delta = 8.53$) compared to $\delta = 5.30$ and $\delta = 5.02$ (as singlets) for the methylene (6-CH₂) protons of **3** and **6**. Also the isomer showed a broad band $\delta = 11.0-11.6$, exchangeable with deuterium oxide. These spectral observations, together with mechanistic considerations, led to the postulation of a hemiacetal structure **8** for the isomeric product.

However, there exists the possibility that the 6-CH proton of **8** may be split by the 6-OH proton, which would be analogous to that recently reported (7) for a 5-hydroxyhydantoin compound. Thus the nmr spectrum of the solution of **8** in DMSO-*d*₆ was re-run in the presence of added deuterium oxide and the pair of doublets ($\delta = 8.53$ and 9.01) attributed to 6-CH and 7-CH respectively remained unchanged. Since the 6-CH doublet did not collapse to a singlet (in the presence of deuterium oxide), the 6-CH splitting cannot be ascribed to the presence of the 6-COH proton and the previous spectral analysis appears valid for structure **8**.

If the hemiacetal structure **8** is valid, then in a favorable environment evidence of tautomeric carboxaldehyde compound (**9**) may be ascertainable (see Scheme 2). Also the observed value of $\delta = 8.53$ for the (6-CH) proton could possibly represent the carboxaldehyde proton instead of the hemiacetal proton. However, the

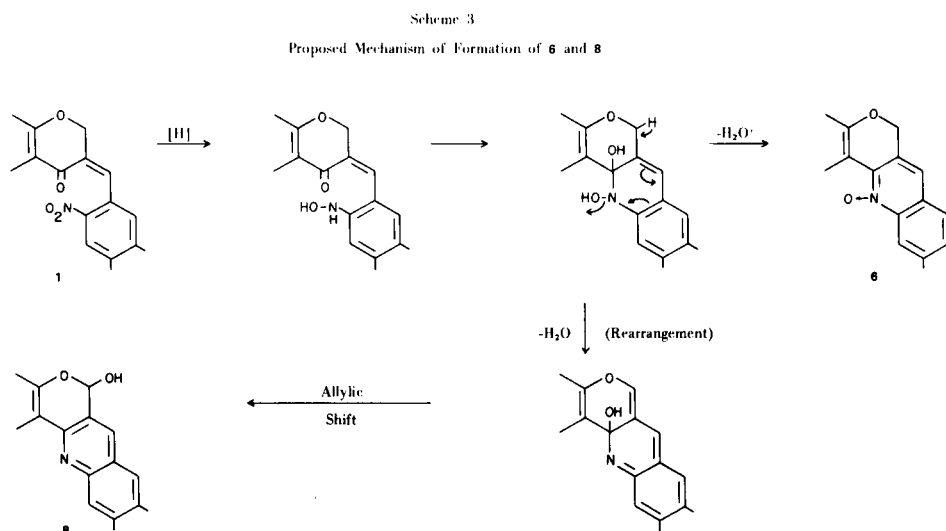
model compound 3-quinolinecarboxaldehyde exhibits the carboxaldehyde proton at $\delta = 11.1$ (8), and other aromatic aldehydes fall in the 10 to 11 ppm region (9). Therefore, since acetal protons are observed in the 7-9 ppm region the hemiacetal structure for **8** remains valid.

Furthermore, the infrared absorption spectrum of the isomeric product (in chloroform), with absorption at $2.9-3.3 \mu$ (OH) but with the absence of carboxaldehyde absorption in the $5.8-6.1 \mu$ region, strongly supports hemiacetal structure **8**. Also the mass spectrum of **8** is consistent with the hemiacetal form.

However the presence of tautomeric carboxaldehyde (**9**) was indeed established through preparation of the unsymmetrical dimethylhydrazone derivative (**10**) of **9** in 45% yield. The nmr spectrum of **10** gave a pattern very similar to that of **8**, with a singlet at $\delta = 2.52$ [=NH(CH₃)₂] and a singlet at 12.75 (OH, exchanged with deuterium oxide).

Although the acetoxy derivative of **8** was easily prepared by heating **8** in acetic anhydride, again the predominant form (**11** or **12**) of the product (acetal or carboxaldehyde) must be considered. The infrared absorption shows the expected acetoxy absorption at 5.7μ with strong absorption at 6.05μ (possibly due to the carboxaldehyde group). The acetoxy derivative (**11** or **12**) showed the same nmr pattern as that of **8**, with the expected singlet for (OOCCH₃) ($\delta = 1.86$), and again the "acetal" proton appears as a doublet at $\delta = 8.39$, instead of a "carboxaldehyde" proton (10-11 ppm region). Therefore, the physical data supports structure **11** for the acetoxy-derivative of **8**.

Finally a mechanism for the formation of the products **6** and **8** observed in the chemical reduction of **1** is proposed as shown in Scheme 3.



EXPERIMENTAL

Infrared spectra were obtained with a Perkin-Elmer Infracord 137; nmr spectra were determined using tetramethylsilane as an internal standard on a Varian A-60A spectrometer; the mass spectroscopy data were obtained on a Hitachi-Perkin Elmer RMU-7 Spectrometer at Northern Illinois University, and the melting point data were obtained on a Fisher-Johns hot stage and are uncorrected.

2,9,10-Trimethoxy-6a,7,12,12a-tetrahydro-6H-[1]benzopyrano[4,3-b]quinoline (**2**).

A mixture of **1** (120 g., 0.32 mole), methanol (800 ml.), and 5% palladium/carbon (50% water) (9 g.) was subjected to hydrogenation at 40 psig. Hydrogen uptake of 1.52 moles (93% of theory) was observed over a 24 hour period, using mild cooling to maintain the temperature below 45°. The reaction mixture was cooled overnight and filtered. The product was extracted from the catalyst with DMF (charcoal) (600 ml.) warmed on a steam bath. The extract was cooled in the refrigerator over the weekend, and the resultant cream-colored, crystalline product was collected by filtration and washed with 2-propanol, ether; m.p. 181-183°, yield, 36 g. (34%); ir (Nujol) μ : 3.02 (NH); nmr (deuteriochloroform) (δ): 1.8-2.9 (m, 3, 6a-CH, 7-CH₂); 3.65 (broad s, 1, NH, exchanged with deuterium oxide); 3.9-4.5 (m, 3, 5-CH₂, 12a-CH); 6.38, 6.61 (2s, 2, aromatic C-H); 6.7-7.0 (m, 3, aromatic C-H).

Anal. Calcd. for C₁₉H₂₁NO₄: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.92; H, 6.49; N, 4.23.

Direct Dehydrogenation of **2** to **3**.

A mixture of **2** (44 g., 0.20 mole), 95% ethanol (ether) (450 ml.), and 5% palladium/carbon (4.0 g.) was refluxed for 21 hours with mechanical stirring. The reaction mixture was filtered hot and the filtrate refrigerated overnight. The resultant white crystalline solid was collected by filtration and washed with 95% ethanol (ether), ether, m.p. 175-177°, yield, 6 g. Additional product (30 g.), m.p. 174-176°, was recovered from the catalyst-product mixture *via* recrystallization from nitromethane (200 ml.); total yield, 36 g. (82%); ir (Nujol) μ : 6.2 and 6.4 μ (aromatic); nmr (DMSO-d₆) (δ): 3.85, 3.92, and 3.97 (3s, 9, CH₃O); 5.30 (s, 2, 6-CH₂); 6.96, 6.98, 7.26, 7.42, and 7.95 (5s, 5 aromatic C-H); 7.84 (t, 1, heteromatic C-H).

Anal. Calcd. for C₁₉H₁₇NO₄: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.48; H, 5.19; N, 4.30.

The By-product (**3**) of the Synthesis of **2**.

The filtrate from the above isolation of **2** was stirred with water (880 ml.) for 5 hours, and the resultant solid was collected by filtration and washed with 2-propanol, ether, yield, 26.8 g. Recrystallization from nitromethane (450 ml.) gave **3**, m.p. 155-162°, yield, 17.6 g. (17%); the ir (Nujol) absorption spectrum was identical to that of authentic **3**.

Catalytic Reduction of **1** in Presence of Acid.

A mixture of **1** (18.6 g., 0.050 mole), methanol (150 ml.), and 5% palladium/carbon (50% water) (6.0 g.), and methanolic hydrogen chloride (4.0 ml.) was subjected to hydrogenation at 44 psig over 24 hours. The reaction mixture was refrigerated for 2 hours, and the product plus catalyst was collected and washed with cold 2-propanol, yield, 18.0 g. The crude product was recrystallized from nitromethane (800 ml.), basified in the cold with 10% sodium hydroxide (30 ml.), and the product was collected by filtration and washed well with cold water, 2-propanol

and ether, yield, 5.3 g. (30%). A sample (1.0 g.) of the product was recrystallized from methanol, m.p. 188-190°.

Anal. Calcd. for C₁₉H₁₇NO₄·2C₁₉H₁₇NO₅·HCl: C, 65.92; H, 5.05; N, 4.05; Cl, 3.41. Found: C, 65.59; H, 5.02; N, 4.04; Cl, 3.63.

The above mixed hydrochloride was basified with 10% aqueous sodium carbonate, warmed on the steam bath with stirring for 5 minutes and the resultant free base was collected by filtration and washed with cold water, 2-propanol, and ether. An infrared absorption spectrum was determined in a chloroform solution of the dried product; the infrared absorption was identical to that determined on a synthetic mixture (1:2 molar) of **3** and **6**. Also a direct comparison of tlc (on Eastman Silica Gel 6060, developed with chloroform) values was made on the product mixture and the synthetic mixture of **3** and **6**; identical R_f values of 0.48 and 0.78 were determined for each.

2,9,10-Trimethoxy-6H-[1]benzopyrano[4,3-b]quinoline 12-Oxide (**6**).

A mixture of **3** (41 g., 0.12 mole) in 95% ethanol (methanol) (450 ml.) was treated with *m*-chloroperbenzoic acid (22 g., 0.13 mole), refluxed for 4.5 hours, and cooled for 3 hours. The resultant orange solid was washed with 2-propanol, ether, m.p. 169-173°, yield, 37 g. (90%). Recrystallization from methanol (charcoal) (3700 ml.) gave **6**, m.p. 191-194°, yield, 23 g. (56%); ir (Nujol) μ : no OH observed; nmr (deuteriochloroform) (δ): 3.92, 3.97, and 4.09 (3s, 9, CH₃O); 5.02 (s, 2, 6-CH₂); 6.91, 6.94, 6.98, 7.18, and 8.15 (5s, 5, aromatic C-H); 9.38 (t, 1, heteromatic C-H).

Anal. Calcd. for C₁₉H₁₇NO₅: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.13; H, 5.04; N, 4.05.

6a,7,12,12a-Tetrahydro-2,9,10-trimethoxy-12-(*N*-methylcarbamoyl)-6H-[1]benzopyrano[4,3-b]quinoline (**7**).

A mixture of **2** (66 g., 0.20 mole) and benzene (1500 ml.) was refluxed for 1.5 hours, removing water *via* a Dean-Stark trap. The slurry was cooled, treated with triethylamine (4 ml.) and methyl isocyanate (57 g., 1.0 mole), and refluxed for 23 hours. The reaction mixture was concentrated to one-third volume, refrigerated overnight, and the resultant white, crystalline product was collected by filtration and washed well with 2-propanol, ether, m.p. 181-183°, yield, 66 g. (86%); ir (Nujol) μ : 2.93 (NH); 6.03 (C=O); nmr (deuteriochloroform) (δ): 1.9-2.7 (m, 3, 6a-CH, 7-CH₂); 2.81 (d, 3, CH₃N, s after exchange with deuterium oxide); 3.77, 3.85, and 3.87 (3s, 9, CH₃O); 4.1-5.0 (m, 3, 6-CH₂, 12a-CH); 6.6-7.0 (m, 5, aromatic C-H); 5.03 (s, 1, NH, exchanged with deuterium oxide).

Anal. Calcd. for C₂₁H₂₄N₂O₅: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.60; H, 6.37; N, 7.26.

6-Hydroxy-2,9,10-trimethoxy-6H-[1]benzopyrano[4,3-b]quinoline (**8**).

To a mixture of **1** (200 g., 0.54 mole) in a solution of methanol (800 ml.) and cyclohexene (800 ml.) was added 5% palladium/carbon (50% water) (90 g.). The slurry was refluxed for 24 hours, with mechanical stirring, and filtered while still hot. The filtrate was seeded with product, stored overnight at room temperature, and the resultant yellow, crystalline solid was collected by filtration and washed with methanol, m.p. 149-156°, yield, 122 g. (61%). Recrystallization from acetone (2500 ml.) gave product (37 g., 20%) which melted at 158-163°. Recrystallization from 80% methanol (DMF) gave analytically pure product, m.p. 173-175°, yield, 24 g. (13%); ir (Nujol) μ : no OH or CHO observed;

ir (chloroform) μ : 3.0-3.2 (broad, weak, OH); no CHO observed; nmr (DMSO- d_6) (δ): 3.74, 3.94, and 4.00 (3s, 9, CH₃O); 7.00-7.10 (m, 3, aromatic C-H); 7.49, 7.57 (2s, 2, aromatic C-H); 8.53 (d, J = 2 Hz, 1, 6-CH); 9.02 (d, J = 2 Hz, 1, heteromatic C-H); nmr (deuteriochloroform) (δ): 11.0-11.6 (broad, 1, OH, exchanged with deuterium oxide); mass spectroscopy: m/e 339 (M⁺), 323 (M-O), 309 (M-HCOH-CH₃), 189 (M-CH₃OC₆H₄OCHOH), 161 (M-OH-di[OCH₃]C₆H₂[N]CH).

Anal. Calcd. for C₁₉H₁₇NO₅: C, 67.75; H, 5.05; N, 4.13. Found: C, 67.28; H, 5.01; N, 4.11.

By-products (**3** and **6**) of the Synthesis of **8**.

The initially isolated product (m.p. 149-156°) in the above synthesis of **8** exhibited an ir absorption spectrum (chloroform) nearly identical to that of authentic **8**, except for weak absorption at 11.0 μ indicative of the presence of **3**.

The filtrate of the 149-156° product was cooled and the resultant yellow solid (A) was collected by filtration; m.p. 144-151°, yield, 15 g. Recrystallization of the 144-151° product from 20% DMF (2-propanol) (175 ml.) gave a yellow, crystalline product, m.p. 152-173°, yield, 9 g. The ir absorption spectrum (chloroform) of the 152-173° product was identical to the ir absorption spectrum (chloroform) of a synthetic mixture of 1:1 authentic **3** and **6**.

From the cooled filtrate of the above prepared 173-175° product **8**, a yellow crystalline solid (m.p. 160-170°) was isolated. **8**, a yellow crystalline solid (m.p. 160-170°) was isolated. Subsequently, the cooled, concentrated filtrate of the 160-170° product provided another yellow, crystalline product, which exhibited an ir absorption spectrum (chloroform) identical to that of the synthetic mixture (1:1) of **6** and **8**.

2-(2-Hydroxy-5-methoxyphenyl)-6,7-dimethoxy-3-quinoline-carboxaldehyde 1,1-Dimethylhydrazone (**10**).

A mixture of **8** (40 g., 0.12 mole) and absolute alcohol (320 ml.) was treated with 1,1-dimethylhydrazine (32.0 ml., 0.42 mole) and heated on the steam bath for 17 hours with mechanical stirring. The reaction solution was filtered hot to remove 1 g. of an insoluble material, concentrated under reduced pressure to a volume of 50 ml. and cooled in the refrigerator for 2 hours. The resultant yellow, crystalline product was collected by filtration, washed with cold absolute ethanol (5 x 5 ml.), 2-propanol (10 ml.), ether, m.p. 147-149°, yield, 21 g. (46%); ir (chloroform) μ : 3.25 (OH, broad); nmr (deuteriochloroform) (δ): 2.52 (s, 6, NN(CH₃)₂); 3.56, 4.03, and 4.07 (3s, 9, CH₃O); 6.44-6.94 (m, 3, aromatic C-H); 7.11, 7.52 (2s, 2, aromatic C-H); 7.99 (d, J = 2 Hz, 1, 3-CH); 8.74 (d, J = 2 Hz, 1, heteromatic C-H).

Anal. Calcd. for C₂₁H₂₃N₃O₄: C, 66.12; H, 6.08; N, 11.02. Found: C, 66.02; H, 6.12; N, 11.11.

2,9,10-Trimethoxy-6H-[1]benzopyrano[4,3-b]quinolin-6-yl Acetate (**11**).

A solution of **8** (30 g., 0.088 mole) and acetic anhydride (14.5 ml.) was heated on the steam bath overnight. The reaction solution was concentrated under reduced pressure to one-half volume and cooled in an ice bath. The resultant crystals were collected by filtration and washed with cold acetic anhydride (50 ml.). The crystals were treated with 2-propanol (40 ml.), cooled, collected by filtration, and washed with cold 2-propanol (60 ml.), ether, m.p. 163-165°, yield, 30 g. (89%); ir (Nujol and chloroform) μ : 5.7 (CH₃COO); 6.05; nmr (deuteriochloroform) (δ): 1.92 (s, 3, COCH₃); 3.82, 4.00, and 4.06 (3s, 9, CH₃O); 7.13 (s, 4, aromatic C-H); 7.52 (s, 1, aromatic C-H); 8.39 (d, 2 Hz, 1, -O-CH-O-); 9.16 (d, 2 Hz, 1, heteromatic C-H); no exchange with deuterium oxide was observed.

Anal. Calcd. for C₂₁H₁₉NO₆: C, 66.13; H, 5.02; N, 3.67. Found: C, 66.20; H, 5.05; N, 3.66.

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REFERENCES AND NOTES

- (1) R. H. Hauadence, G. K. Hughes and F. Lions, *J. Proc. Roy. Soc., N. S. Wales*, **72**, 273 (1939); *Chem. Abstr.*, **33**, 6841² (1939).
- (2) J. Algar and T. A. M'Cullagh, *Proc. Roy. Irish Acad.*, **40B**, 84 (1931); *Chem. Abstr.*, **26**, 459⁵ (1932).
- (3) Part I, *J. Heterocyclic Chem.*, **13**, 1177 (1976).
- (4) P. Pfeiffer and G. von Bank, *J. Prakt. Chem.*, **151**, 319 (1938); *Chem. Abstr.*, **33**, 1735^{5,8} (1939).
- (5) G. Kempfer and S. Hirschberg, *Chem. Ber.*, **98**, 419 (1965); *Chem. Abstr.*, **63**, 1779a (1965).
- (6) J. W. Schulenberg and S. Cornrich, *J. Chem. Eng. Data*, **13**, 574 (1968).
- (7) R. L. White and T. J. Schwan, *J. Pharm. Sci.*, **65**, 135 (1976).
- (8) "The Aldrich Library of NMR Spectra," Vol. IX, C. J. Pouchert and J. R. Campbell.
- (9) "NMR Spectra Catalog," Copyright, Varian Associates, 1962, examples 148 and 151.
- (10) E. A. Fehnel, *J. Org. Chem.*, **31**, 2899 (1966).