Transfer Hydrogenations of Furocoumarin Derivatives[1]

Ned D. Heindel,* Natalie Foster, and Mridula Choudhuri

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015

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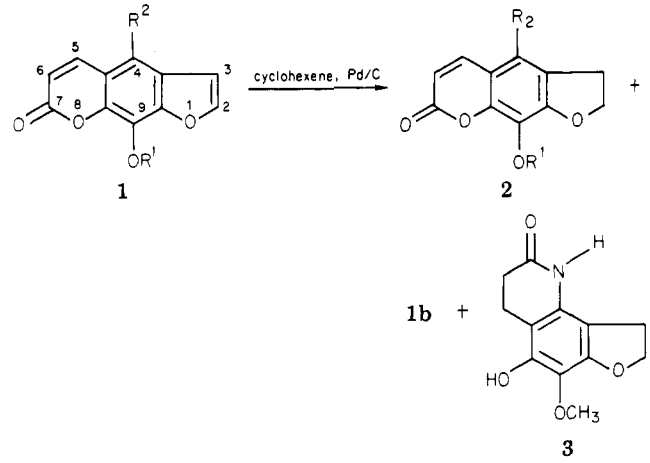
Radioiodinations and radiofluorinations through the diazotization of amines and halide decomposition of the intermediate diazonium ions have become popular, general methods for the synthesis of radioactive pharmaceuticals used in biological studies.[2-6] We have found that nitro-containing drugs can often be simply and smoothly reduced to the aryl amines needed for the diazotization by the selective rapid-transfer reduction.[6] In this method cyclohexene in refluxing ethanol is used as a hydrogen donor under catalysis by palladium supported on carbon.[7] Attempts, however, to apply the reaction to 4-nitro-9-methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one (**1a**), a member of a family of dermal photosensitizing agents known as psoralens or furocoumarins, illustrates the complexity to which the reaction may sometimes be prone.

After 60 min of contact between the palladium catalyst and **1a** in cyclohexene and ethanol, the expected 4-amino-9-methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one (**1b**) was obtained as well as the ring-saturated analogue, 2,3-dihydro-4-amino compound (**2b**), and the reduced rearranged 4-methoxy-5-hydroxy-1,2,6,7-tetrahydro-9*H*-furo-[2,3-*h*]quinolin-8-one (**3**). These latter products clearly illustrated the ability of the transfer hydrogenation to reduce a heteroaromtic system under mild reaction conditions (see Scheme I). Earlier studies with ethylenic hydrocarbons such as indene, acenaphthylene, stilbene, crotonic acid, and allylbenzene did show that long reflux times (16–80 h) could bring about the cyclohexene transfer hydrogenation of nonbenzenoid unsaturation.[8] Indeed, the nonbenzenoid bonds in coumarin[9] and in 2-phenylchromenones[10,11] were reduced in unspecified yields by prolonged heating in limonene or in tetralin, but the milder conditions (refluxing ethanol containing cyclohexene) suggested by Entwistle[7] have not been reported to reduce heterocyclic unsaturation.

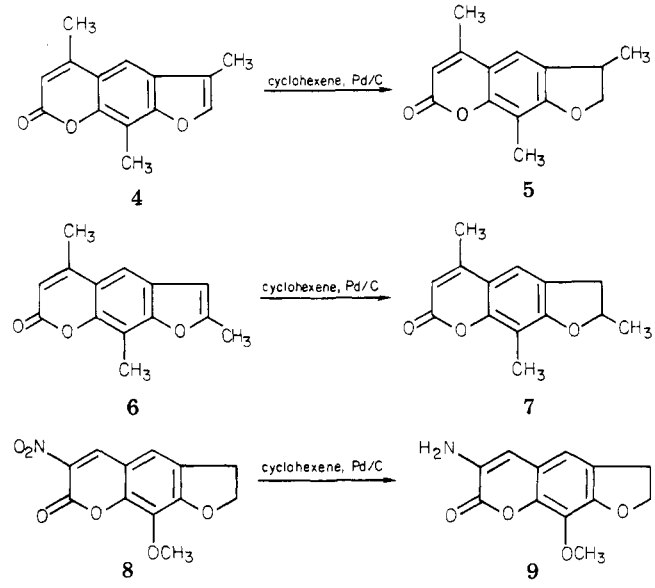
After the observation of the reduction of **1a**, we employed these reaction conditions on several other furocoumarins with similarly excellent yields on hydrogenation of the furano bond; **1b–d**, **4**, and **6** were reduced to their correponding dihyro analogues **2b–d**, **5**, and **7** in yields of 64–77% (see Scheme II). A nitro-containing dihydro compound (**8**), was reduced to the amine **9** in 77% yield

Scheme I[a]



[a] a, $R^1 = CH_3$; $R^2 = NO_2$. b, $R^1 = CH_3$; $R^2 = NH_2$. c, $R^1 = CH_3$; $R^2 = H$. d, $R^1 = R^2 = H$.

Scheme II



with no detectable further reduction of the coumarin ring unsaturation. In fact, even after reflux of 1.5 h coumarin reduction was observed only when it accompanied ring-opening/reclosing as in the formation of **3** from **1a**/**1b**. Catalytic hydrogenation (Pd/C) of **6** with 1 equiv of H_2 reduced the 2,3- and the 5,6-unsaturation, and a 36% yield of **7** mixed with unreacted **6** and some tetrahydro compound was obtained.[12] Transfer hydrogenation is more easily controlled.

To follow more precisely the progress of the reduction, a liquid chromatographic method was developed with conditions that cleanly separated the reaction components. An untraviolet detector at 254 nm monitored the effluent from a reverse-phase C-8 column, and concentrations were determined by correction of peak areas with the previously determined extinction coefficients of the purified compounds. All reductions except that of **1b** were essentially completed after 10 min of reflux. Traces of starting material (5–10%) remained, but the concentrations did not alter with time and may reflect a hydrogenation–dehydrogenation equilibrium. The yields detected for **2c–d**, **5**, and **7** from their correponding fully unsaturated furo-

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coumarins were greater than 85%, although isolated yields were somewhat less.

Reduction of **1a** and **1b** revealed the complexity already known to exist from product isolation studies. After 10 min, **1a** had produced 50% of the unsaturated amine **1b**, 40% of the dihydro amine **2b**, and 10% of the denitrated dihydro compound **2c**. Only a trace (<1%) of starting material **1a** remained. After 60 min, the major product (ca. 85%) was **2b**, with 5% **1b** and 10% **2c**. After 1.5 h, a barely detectable concentration (1–2%) of **1b** remained, **2b** and **2c** were unchanged, and 2–3% of **3** was present. In a second experiment, when purified **1b** was subjected to hydrogen-transfer reduction, it reduced more slowly than other furocoumarins studied. After 10 min, 60% of **1b** remained while 30% of the 2,3-dihydro compound **2b** and 10% of the hydrogenolyzed **2c** had formed. After 30 min, only 10% of **1b** was left, the yield of **2c** remained unchanged, and the concentration of the dihydro amine **2b** had reached 80%. After 1.5 h, starting material **1b** was virtually indetectable, ring-hydrogenated amine **2b** had reached 88%, **2c** remained unchanged at 10%, and a 1-2% quantity of **3** was evident.

Since reductive deaminations by transfer hydrogenation are well-known,[11] the formation of small quantities of **2c** from both **1a** and **1b** is not surprising. Such deamination, however, must occur rapidly and either poison the catalyst or saturate available reaction sites since further deamination does not occur. The formation of the dihydro amine **2b** at the expense of **1b** indicates that nitro group reduction is more rapid than hydrogenation of the furan bond, and the slower overall reduction of **1b** in a second experiment confirms the conclusion. In other studies, amino-containing compounds bearing reducible nitro groups reacted sluggishly[7,13] and the possibility of a stereochemically unfavorable absorption on the catalyst surface has been suggested.[13] The furanoquinolinone **3** that forms at long contact times probably reflects an initial ring-opening of the coumarin ring by water or ethanol, followed by a reduction, and a subsequent cyclization. No reduced coumarins were detected in these reaction studies, and previous work has shown high temperatures (>140 °C) to be required to transfer hydrogenate coumarins and chromenones.[9,10] However, refluxing cyclohexene/palladium has served to reduce smoothly cinnamic acid to β-phenylpropionic acid.[8]

Experimental Section

^{1}H NMR spectra were obtained on a JEOL-FX90Q spectrometer. Infrared spectra were obtained in 1% KBr disk on a Perkin-Elmer 283 infrared spectromter. Melting points were obtained in capillaries in a Thomas-Hoover apparatus and are reported uncorrected. Elemental analyses were provided by Dr. G. I. Robertson, Microanalytical Laboratory, Florham Park, NJ. Furocoumarin starting materials **1c**, **1d**, **4**, and **6** were provided by Elder Pharmaceutical Co., Bryan, OH.

HPLC Evaluation of Product Mixtures. A solution of 0.100 g of the psoralen dissolved in 25 mL of refluxing 95% ethanol and 0.25 mL of cyclohexene was treated to the addition of 0.25 g of 10% palladium on carbon catalyst. Three-milliliter aliquots of the reaction suspension were withdrawn at each time indicated (t_0 being the addition of the Pd/C to the other coreactants), filtered, evaporated to dryness, and redissolved in a minimum of HPLC-grade methanol. Mixtures were analyzed on a C-8 reverse-phase analytical column with 37:63 methanol/water as the moving phase and a flow rate of 2.5 mL/min. A Perkin-Elmer Series 2 Liquid Chromatograph with an LC-75 variable-wavelength spectrophotometric detector set at 254 nm was employed. Peaks were identified by comparison of retention times and reinforcement with known samples. Quantifications were based on peak areas corrected by the previously evaluated extinction coefficients of the purified components.

General Procedure for Preparative Transfer Reductions. The required furocoumarin (1.00 g of **1a–d**, **4**, **6**, **8**) was dissolved in 100 mL of refluxing 95% ethanol. To this boiling solution were added 2.5 mL of cyclohexene and a suspension of 2.45 g of 10% palladium on carbon in 15 mL of 95% ethanol. The mixture was stirred at reflux for the indicated time, filtered, evaporated in vacuo, and the product(s) isolated by fractional crystallization from 95% ethanol.

Reduction of 1a. Utilizing the preparative transfer hydrogenation with 10 min of reflux, a mixture of **1b** and **2b** was obtained. Successive fractional crystallization from 95% ethanol gave 0.40 g (44%) of **1b**, mp 242–243 °C (lit.[14] mp 234–235 °C) whose mixture melting points and infrared and ^{1}H NMR spectra were identical with those of authentic material obtained by the reported stannous chloride reduction of **1a**. The other product (**2b**), the more soluble component in the 95% ethanol, was isolated in 31% yield (0.29 g): mp 240–242 °C (lit.[15] mp 232–234 °C); ^{1}H NMR (Me_2SO-d_6) δ 3.04 (t, 2, CH_2, J = 9 Hz), 3.76 (s, 3, OCH_3), 4.71 (t, 2, CH_2, J = 9 Hz), 5.82 (br s, 2, NH_2, D_2O exchangeable), 6.02 (d, 1, =CH, J = 9.5 Hz), 9.24 (d, 1, =CH, J = 9.5 Hz).

Under identical reaction conditions but with 1 h of reflux, the most soluble component precipitating from the 95% ethanol was 5-hydroxy-4-methoxy-1,2,6,7-tetrahydro-9*H*-furo[2,3-*h*]quinolin-8-one (**3**), as a silver-white solid: 0.12 g, 13% yield; mp 267–268 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.10–2.55 (m, 4, CH_2CH_2), 2.81 (t, 2, CH_2, J = 8.5 Hz), 3.48 (s, 3, OCH_3) 4.30 (t, 2, CH_2, J = 8.5 Hz), 8.53 (s, 1, OH, exchangeable rapidly in D_2O), 9.42 (br s, 1, NH, exchangeable slowly in D_2O). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.01; H, 5.54; N, 5.72. Although **1b** and **2b** were also present in the reaction mixture (by HPLC), they were not isolated in this 1-h reduction.

Reduction of 1c. Following 30 min of reflux under the standard preparative reaction conditions, removal of the catalyst and concentration in vacuo yielded 0.72 g (71%) of pale yellow needles of 2,3-dihydro-9-methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one (**2c**): mp 164–165 °C (lit.[16] mp 163 °C); ^{1}H NMR ($CDCl_3$) δ 3.11 (t, 2, CH_2, J = 8 Hz), 3.78 (s, 3, OCH_3), 4.58 (t, 2, CH_2, J = 8 Hz), 6.11 (d, 1, =CH, J = 10 Hz), 7.10 (s, 1, ArH), 7.78 (d, 1, =CH, J = 10 Hz).

Reduction of 1d. When 1.00 g of 9-hydroxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one (**1d**) was reacted at reflux temperature for 30 min as described above, evaporation of the filtered reaction mixture gave, after recrystallization from 95% ethanol, 0.77 g (77%) of off-white solid identified as 2,3-dihydro-9-hydroxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one (**2d**): mp 204–205 °C (lit.[16] mp 202 °C); ^{1}H NMR (Me_2SO-d_6) δ 3.19 (t, 2, CH_2, J = 8 Hz), 4.65 (t, 2, CH_2, J = 8 Hz), 6.20 (d, 1, =CH, J = 9 Hz), 7.00 (s, 1, ArH), 7.88 (d, 1, =CH, J = 9 Hz), 9.69 (s, 1, OH).

Reduction of 4. The reduction of **4** by the above method gave **5** in 64% yield: mp 131–133 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.35 (d, 3, C_3 CH_3, J = 8 Hz), 2.25 (s, 3, C_9 CH_3), 2.37 (d, 3, C_5 CH_3, J = 0.5 Hz), 3.61 (m, 1, C_3 H), 4.19 (dd, 1, C_2 β-H, J = 9 Hz), 4.80 (dd, 1, C_2 α-H, J = 9 Hz), 6.05 (d, 1, C_6 H, J = 0.5 Hz), 7.19 (s, 1, C_4 H). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.12. Found: C, 73.26; H, 5.97.

Reduction of 6. From 1.00 g of **6** was obtained 70% of the trimethyldihydro analogue **7** mp 159–161 °C (lit.[12] mp 159.5–160.5 °C); ^{1}H NMR ($CDCl_3$) δ 1.49 (d, 3, C_2 CH_3, J = 8 Hz), 2.24 (s, 3, C_9 CH_3), 2.35 (d, 3, C_5 CH_3, J = 0.5 Hz), 2.90 (dd, 1, C_3 β-H, J = 9 Hz), 3.31 (dd, 1, C_3 α-H, J = 9 Hz), 5.01 (m, 1, C_2H), 6.05 (d, 1, C_6 H, J = 0.5 Hz) 7.18 (s, 1, C_4 H).

Reduction of 8. Upon reduction of **8**[15] by the selective rapid-transfer method, a 77% yield of **9**, mp 154–155 °C (from 95% ethanol) was obtained: ^{1}H NMR ($CDCl_3$) δ 3.17 (t, 2, CH_2, J = 8 Hz), 3.20–3.40 (br s, 2, NH_2, exchangeable in D_2O), 3.97 (s, 3, OCH_3), 4.58 (t, 2, CH_2, J = 8 Hz), 6.56 (s, 1, C_5 H), 6.70 (s, 1, C_4 H). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.76; N, 6.01. Found: C, 61.82; H, 4.69; N, 5.78.

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Registry No. **1a**, 1930-56-9; **1b**, 49739-65-3; **1c**, 298-81-7; **1d**, 2009-24-7; **2b**, 1930-59-2; **2c**, 3779-03-1; **2d**, 68123-30-8; **3**, 86885-06-5; **4**, 15294-25-4; **5**, 73640-81-0; **6**, 3902-71-4; **7**, 21902-10-3; **8**, 1930-58-1; **9**, 86885-07-6; cyclohexene, 110-83-8.

Electrophilic Addition of OsO_4 to 25-Hydroxycholecaliferol and Its 3,5-Cyclo Derivative[1]

Herbert E. Paaren,[2] Heinrich K. Schnoes,* and Hector F. DeLuca

Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin—Madison, Madison, Wisconsin 53706

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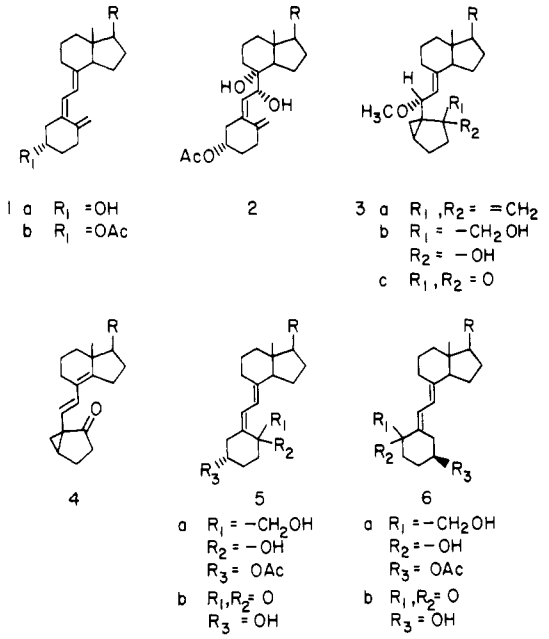
The organic chemistry of vitamin D has been largely confined to the synthesis and characterization of many of its biologically revelant metabolites, with the main efforts being directed at 1α-hydroxylation and side-chain modification schemes.[3] The chemistry of the conjugated triene, which typifies the vitamin D skeleton, and methods for its selective modification have not been explored systematically, although the s-cis character of the 5,6- and 10(19)-double bonds has been exploited for the formation of adducts with $Fe_2(CO)_9$[4] and in reactions with dienophiles (SO_2, triazoline, and singlet oxygen).[5-8] Hydroboration of the vitamin with the bulky borohydride 9-BBN exhibits high regioselectivity for the 10(19)-double bond of the triene and gives the 19-hydroxy-10(19)-dihydrovitamin analogues in excellent yields.[9]

In connection with our biochemical work, we were interested in preparing chemically or photochemically reactive probes (affinity labels) for the various macromolecular binding protein (e.g., the D-transport protein, or the cytosolic receptor protein) of the vitamin D endocrine system. We report here on the reactions of 25-hydroxycholecalciferol and its cyclovitamin derivative with osmium tetraoxide in pyridine that illustrate aspects of the electrophilic chemistry of the vitamin D triene and led to two 10-oxo derivatives with potential utility as covalent markers in biochemical systems.

When 25-hydroxycholecalciferol 3-acetate (**1b**) in pyridine was treated with a 1.2-fold excess of a freshly prepared OsO_4/pyridine reagent (100 mg/mL) at room temperature, a rapid reaction ensued and TLC analysis revealed the total absence of starting material within 10 min. A 75% yield of compound **2** was obtained, characterized as the 7,8-vicinal diol by NMR and mass spectral analysis. The stereochemistry of the 7,8-diol can be assigned by assuming α-face attack of the osmium reagent due to the presence of the axial β-face C-18 methyl group. The downfield NMR shift (from 0.54 to 0.80 ppm) for the C-18 methyl group in the 7,8-diol product also argues for an α-orientation of the 8-hydroxyl group.



The unique regiospecificity of this reaction on the normal vitamin skeleton changes dramatically when the 3,5-cyclovitamin analogue **3a** is utilized as a substrate. When **3a** was treated as above, the reaction was equally rapid and afforded a predominant product in 70% yield. NMR and mass spectroscopy established the cyclovitamin adduct as the 10,19-diol **3b**.

The pronounced change in the olefinic reactivity toward osmium tetraoxide can be rationalized on the basis of the known preference for osmic acid addition to strained, but sterically accessible, double bonds.[10-12] The normal vitamin triene possesses a great deal of conformational and rotational flexibility with only the 7,8-double bond rigidly fixed and exocyclic to the C ring. The β-face of the C-D ring system is sterically shielded by the axial orientation of the C-18 methyl group. In the cyclovitamin derivative the steric environment of the 7,8-double bond is drastically altered. The presence of the 6(*R*)-methoxy functionality makes it inaccessible to reagent approach, while 10(19)-olefin is conformationally fixed and strained by the [3.1.0] A-ring system and thus becomes the preferred target for the reagent.

The 10,19-dihydroxycyclovitamin **3b** was envisioned as the precursor for the 10-oxo-19-nor vitamin analogue **5b**. This $\alpha,\beta,\gamma,\delta$-unsaturated ketone (a structural relative of the 10-oxovitamin D_2 analogue previously synthesized as an intermediate in the partial synthesis of vitamin D_2[13]), has all the attributes of an endo-photoaffinity label,[14] i.e., a photoreactive chromophore absorbing at long wavelengths (310 nm) with a high extinction coefficient (15 000) and located on a part of the molecule that is within the binding domain of the macromolecule.

The conversion of the cyclovitamin-10,19-diol to the 10-oxo analogue **3c** was accomplished smoothly by treatment of **3b** with $NaIO_4$ in MeOH. However, reaction of **3c** with glacial HOAc gave diene **4**, resulting from the

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