Synthesis of 5-[(Indol-2-on-3-yl)methyl]-2,2-dimethyl-1,3-dioxane-4,6-diones and Spirocyclopropyloxindole Derivatives. Potential Aldose Reductase Inhibitors†

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Introduction

Aldose reductase is an enzyme found in the eye lens and in a variety of other tissues which display diabetes-associated pathology in humans.[1−3] This enzyme has been implicated in diabetic cataract, and there has been increasing evidence of its involvement in other diabetic complications such as corneal wound healing defects, neuropathy, retinopathy, nephropathy, and platelet aggregation. To treat and prevent such diabetic complications arising from elevated levels of sorbitol, research has focused on the development of potent aldose reductase inhibitors (ARIs).

There have been a number of reports[4] in the literature on structurally diverse ARIs. During previous studies[5] from this laboratory, 5-[(5-fluoroindol-3-yl)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione **3b** displayed high aldose reductase inhibitory activity. On the basis of those studies,[5] certain structural and functional requirements for a good inhibitor were noted. For example, the inhibitory activities of oxindolyl derivatives were better than the corresponding indolyl derivatives and the activity of dioxindolyl derivatives were better than the corresponding oxindolyl derivatives. Thus, it was our aim to synthesize 5-[(oxindol-3-yl)methyl]-2,2-dimethyl-1,3-dioxane-4,6-diones (oxindolyl derivatives of **3b**) and also 5-[(oxindol-3-hydroxy-3-yl)methyl]-2,2-dimethyl-1,3-dioxane-4,6-diones (dioxindolyl derivatives of **3b**) to be able to evaluate them as inhibitors of aldose reductase.

Results and Discussion

Treatment of indoles **1a**−**d** with Meldrum's acid **2** and formaldehyde, following the procedure of Farlow et al.,[6] gave indolyl derivatives **3a**−**d** in 80−96% yield. The indolyl derivatives **3a**−**c** were treated with 1 equiv of *N*-bromosuccinimide in 95% *tert*-butyl alcohol/water following the procedure of Hinman et al.[7] to yield the corresponding oxindolyl derivatives **4a**−**c** in 62−67% yield. Surprisingly, similar treatment of 5-[(5-nitroindol-3-yl)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione **3d** with NBS yielded only the bromo derivative **5** (Scheme 1).

It was also of interest to oxidize the oxindolyl derivatives to the corresponding 2,3-dioxindolyl derivatives. Treatment of oxindolyl derivative **4a** with oxygen[8] in 1 N sodium hydroxide solution did not give the desired dioxindolyl derivative **6** but resulted in the cleavage of the heterocyclic ring to yield aniline derivative **7** in 63% yield. This type of cleavage of an oxindole ring under basic oxidative conditions has precedence in the literature.[9] Consequently, we decided to synthesize the 3-bromooxindolyl derivative and then convert it into the corresponding dioxindole. Treatment of indolyl derivatives **3a** and **3b** with 2 equiv of *N*-bromosuccinimide at room temperature gave only the unusual spirocyclopropane derivatives **8a** and **8b** in 47−52% yield, presumably via the 3-bromooxindolyl intermediate. Although, we managed to isolate 3-bromooxindole derivative **9** under very meticulous conditions (e.g., the reaction workup was done at or below room temperature), our attempted hydrolysis resulted in the isolation of only the spirocyclopropane derivative **8a** (Scheme 2). The 3-bromooxindole derivative **9** was not stable, and NMR studies indicated its slow conversion to the spirocyclopropane derivative **8a**. Further attempts to synthesize dioxinolyl derivative **6** were abandoned.

The structures of spirocyclopropyloxindole derivatives **8a** and **8b** were supported by ^{1}H and ^{13}C spectral data. The ^{1}H NMR of compound **8a** showed two doublets at δ 2.83 and 3.09 due to the cyclopropyl CH_2 group, and the corresponding peaks were observed at δ 2.81 and 3.0 in the ^{1}H spectrum of **8b**. The downfield shifts of the cyclopropyl protons could be attributed to the spatial orientations of these protons. A 3D structure of the skeleton of **8a**, sans the methyl groups for greater clarity, is depicted in Figure1. As suggested by the figure, one of the cyclopropyl protons is situated in the deshielding zone of the ring current as well as one of the carbonyl groups and the other proton is in the deshielding zone of two carbonyl groups. ^{13}C NMR of **8a** and **8b** displayed peaks at δ 21.5 and 21.3, respectively, for the cyclopropyl

† Dedicated to the memory of the late Dr. Louis A. Cohen.

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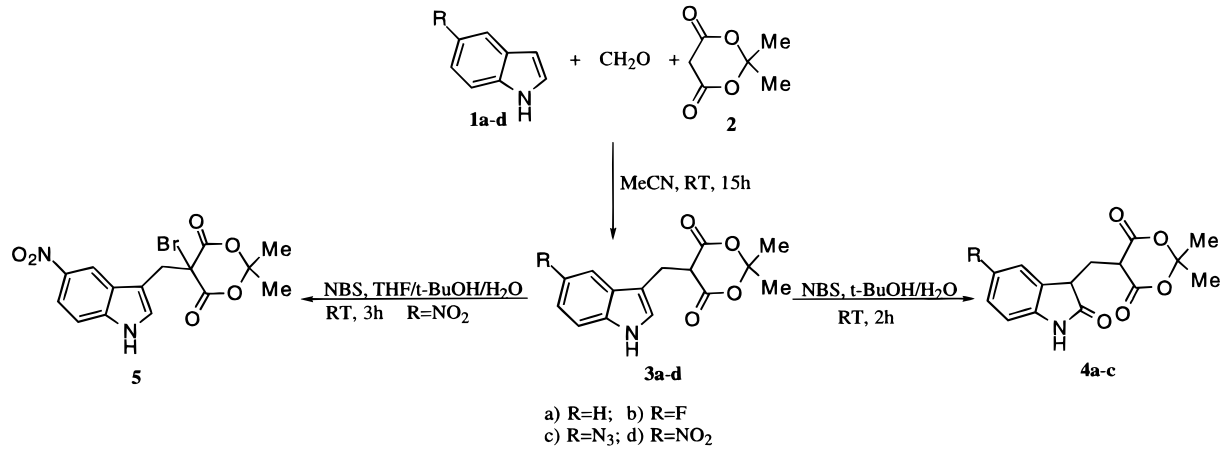
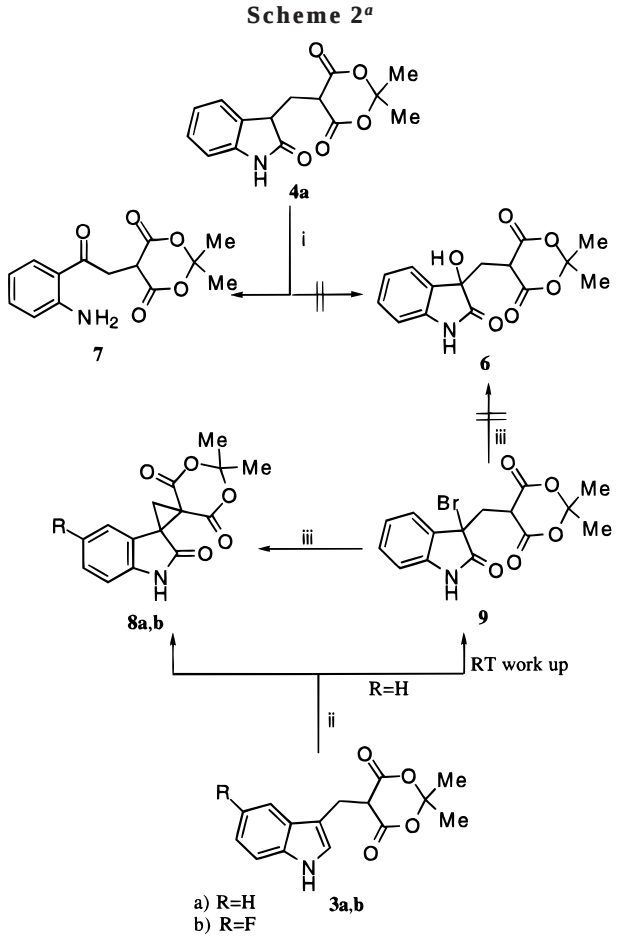
Scheme 1



Scheme 2[a]



[a] (i) 1 N NaOH/air, rt 20 h. (ii) 2NBS, *t*-BuOH/H_2O, rt 3 h. (iii) Dioxane/H_2O, reflux, 2 h (or) MeOH/H_2O/HCl, rt.

methylene carbon. This observation was further corroborated by an APT experiment, which showed that these carbons were attached to an even number of hydrogens.

We also wanted to study the effect of a methyl group at the 3-position of oxindole. Since earlier work[5] from this laboratory indicated moderately high inhibitory activity for dioxindole-3-propionic acid, it was desirable to replace the OH group with the CH_3 group at the three position of oxindole. Thus, 1-acetyl-3-methyloxindole **10** was treated with ethyl acrylate and potassium *tert*-butoxide in *tert*-butyl alcohol, followed by sodium hydroxide in

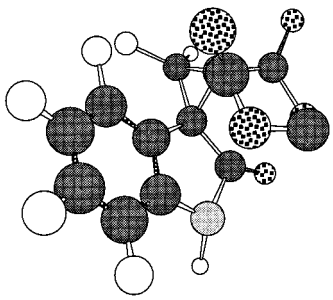
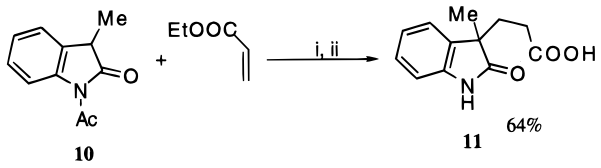


Figure 1.

Scheme 3[a]



[a] (i) *t*-BuOK/*t*-BuOH, rt. (ii) NaOH/aqueous MeOH, rt.

aqueous methanol, to yield 3-methyloxindole-3-propionic acid **11** in 64% yield (Scheme 3).

Aldose reductase inhibitory activity of the oxindole derivatives reported in this paper will be reported in due course. It is expected that the azidoindole and azidooxindole derivatives **3c** and **4c**, respectively, will be of use in photoaffinity labeling studies of AR to learn more about its binding pockets. Such information would help in designing still better inhibitors.

Experimental Section

General Methods. Elemental analyses were done at Atlantic Microlab, Norcross, GA. Silica gel 60 (230−400 mesh) was used for column chromatography.

Synthesis of 5-(Indol-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-diones 3a−d. General Procedure. To a solution of appropriate indole **1a−d** (10 mmol) in CH_3CN (10 mL) were added Meldrum's acid **2**, formaldehyde (37%, 0.81 mL, 10 mmol), and L-proline (0.06 g, 0.5 mmol), and the reaction mixture was stirred at room temperature for 5 h (20 h for **1d**). After removal of the solvent under reduced pressure, the residue was dissolved in warm ethanol or methanol and crystallized.

5-(Indol-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 3a: yield 2.29 g (84%); mp 123 °C (dec) (lit.[6] mp 106−108 °C); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 3H, Me), 1.7 (s, 3H, Me), 3.65 (d, J = 3.2 Hz, 2H, CH_2), 3.77 (t, J = 3.2 Hz, 1H, CH), 7.1−7.21

(m, 3H, arom), 7.32 (d, J = 7.8 Hz, 1H, arom), 7.72 (d, J = 7.8 Hz, 1H, arom), and 8.1 (bs, 1H, NH).

5-(5-Fluoroindol-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione[10] 3b: yield 2.8 g (96%); mp 121−123 °C (methanol); ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 3H, Me), 1.72 (s, 3H, Me), 3.47 (d, 2H, J = 4.8 Hz, CH_2), 4.12 (t, 1H, J = 4.8 Hz), 6.87−6.94 (m, 1H, arom), 7.17 (s, 1H, arom), 7.32−7.36 (m, 2H, arom), and 9.2 (bs, 1H, NH); MS (CI, NH_3) m/z 292 (M + 1). Anal. Calcd for $C_{15}H_{14}NO_4F$: C, 61.85; H, 4.81; N, 4.81; F, 6.53. Found: C, 61.84; H, 4.68; N, 4.66; F, 6.33.

5-(5-Azidoindol-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 3c: yield 2.51 g (80%); mp 160−62 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 3H, Me), 1.7 (s, 3H, Me), 3.6 (d, 2H, J = 4.5 Hz), 3.75 (t, 1H, J = 4.5 Hz), 6.86 (dd, 1H, arom), 7.2−7.4 (m, 3H, arom), and 8.08 (bs, 1H, NH); MS (CI/NH_3) m/z 332 (M + 18). Anal. Calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.26; H, 4.54; N, 17.93.

5-(5-Nitroindol-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 3d: yield 2.5 g (79%); mp 195 °C (dec, methanol) (lit.[11] mp 182 °C); ^{1}H NMR (DMSO-d_6) δ 1.55 (s, 3H, Me), 1.8 (s, 3H, Me), 3.48 (d, 2H, J = 4.5 Hz), 4.87 (t, 1H, J = 4.5 Hz), 7.36 (s, 1H, indole-2H), 7.51 (d, 1H, J = 8.8 Hz), 7.98 (d, 1H, J = 8.8 Hz), 8.67 (s, 1H, arom), and 11.7 (s, 1H, NH); MS (CI/NH_3) m/z 318 (M^+).

Synthesis of 5-(Indol-2-on-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-diones 4a-c. General Procedure. To a solution of the compound **3a**−**c** (1 mmol) in 95% t-BuOH/H_2O (10 mL) was added NBS (0.18 g, 1 mmol) slowly over a period of 20 min. The solution was stirred at room temperature for 2 h and concentrated. The residue was extracted with EtOAc, washed with H_2O (3 × 15 mL), and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was dissolved in the appropriate solvent(s) and crystallized.

5-(Indol-2-on-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 4a: yield 0.19 g (66%); mp 148−49 °C (dec, EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.8 (s, 3H, Me), 1.95 (s, 3H, Me), 2.44−2.53 (m, 1H), 2.61−2.71 (m, 1H), 3.96−4.02 (m, 1H), 4.93−4.96 (dd, 1H), 6.8 (d, 1H, J = 7.5 Hz, arom), 7.07 (t, 1H, arom), 7.22−7.30 (m, 2H, arom), and 7.73 (bs, 1H, NH); MS (CI/NH_3) m/z 290 (M + 1). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.22; H, 5.22; N, 4.81.

5-(5-Fluoroindol-2-on-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 4b: yield 0.19 g (62%); mp 161−62 °C (dec, EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3H, Me), 1.95 (s, 3H, Me), 2.46−2.69 (m, 2H), 4.0 (m, 1H), 6.82−7.07 (m, 3H, arom), and 7.72 (bs, 1H, NH); MS (CI/NH_3) m/z 308 (M + 1). Anal. Calcd for $C_{15}H_{14}NO_5F$: C, 58.63; H, 4.59; N, 4.56. Found: C, 58.60; H, 4.66; N, 4.63.

5-(5-Azidoindol-2-on-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 4c: yield 0.22 g (67%); mp 150−55 °C (dec); ^{1}H NMR ($CDCl_3$) δ 1.8 (s, 3H, Me), 1.9 (s, 3H, Me), 2.43−2.66 (m, 2H, CH_2), 3.98 (dd, 1H), 4.87 (dd, 1H), 6.83−6.97 (m, 3H, arom), and 7.52 (bs, 1H, NH); MS (EI) m/z 330 (M^+). Anal. Calcd for $C_{15}H_{14}N_4O_5$: C, 54.55; H, 4.27; N, 16.96. Found: C, 54.73; H, 4.36; N, 16.75.

Synthesis of 5-(5-Nitroindol-3-ylmethyl)-5-bromo-2,2-dimethyl-1,3-dioxane-4,6-dione 4d. The compound **3d** (0.32 g, 1 mmol) was dissolved in a mixture of THF (10 mL), t-BuOH (5 mL), and H_2O (1 mL). NBS (0.18 g, 1 mmol) was then added, and the reaction mixture was stirred for 3 h. Then the solvents were removed under reduced pressure, and the precipitated solid was filtered, washed with H_2O, and dried. The crude compound **4d** was crystallized from acetone/hexane: yield 0.23 g (58%); mp 154−56 °C (dec); ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 3H, Me), 1.82 (s, 3H, Me), 4.1 (s, 2H), 7.4 (d, 1H, J = 1.7 Hz, arom), 7.6 (d, 1H, J = 9.3 Hz, arom), 8.05 (dd, 1H, arom), 8.72 (d, 1H, J = 1.4 Hz, arom), and 10.98 (bs, 1H, NH); MS (CI/NH_3) m/z 396 and 398 (M^+). Anal. Calcd for $C_{15}H_{13}N_2O_6Br$: C, 45.36; H, 3.3; N, 7.05. Found: C, 45.45; H, 3.36; N, 7.00.

(10) The data for this compound was taken from ref 5.

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Attempted synthesis of dioxindole derivative 6. Air was bubbled through a stirred suspension of compound **4a** (0.1 g, 0.35 mmol) in a 1 N NaOH solution (5 mL) for 20 h at room temperature. The solution was neutralized with a few drops of AcOH at 0 °C, and the precipitated solid was washed with H_2O, dried, and crystallized from EtOAc/hexane. The compound was found to be **7**: yield 0.06 g (63%); mp 155 °C; ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3H, Me), 1.91 (s, 3H, Me), 3.85 (t, 1H, J = 3.63 Hz), 3.93 (d, 2H, J = 3.63 Hz), 6.21 (bs, 2H, NH_2), 6.64−6.72 (m, 2H, arom), 7.3 (m, 1H, arom), and 7.75 (d, 1H, J = 8.2 Hz arom); MS (CI/NH_3) m/z 278 (M + 1). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 60.55; H, 5.41; N, 5.01.

Synthesis of Spirocyclopropane Derivatives 8a and 8b. To a solution of compound **3a** or **3b** (1 mmol) in t-BuOH (19 mL) and H_2O (1 mL) was added NBS (0.36 g, 2 mmol). The reaction mixture was stirred for 3 h at room temperature, whereupon the solvent was removed under reduced pressure. Cold H_2O was added to the reaction mixture, and the precipitated solid was filtered, washed further with H_2O, dried, and crystallized from appropriate solvents.

Spirocyclopropane derivative 8a: yield 0.15 g (52%); mp 270 °C (dec, acetone/hexane); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3H, Me), 1.71 (s, 3H, Me), 2.83 (d, 1H, J = 6.4 Hz), 3.09 (d, 1H, J = 6.4 Hz), 7.0 (d, 1H, J = 7.74 Hz, arom), 7.09 (t, 1H, J = 7.74 Hz, arom), 7.31−7.4 (m, 2H, arom), and 8.05 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.5, 27.0, 29.5, 41.7, 44.9, 106.2, 111.5, 123.5, 124.5, 126, 131, 142, 159.5, 163.5, and 172; MS (CI/NH_3) m/z 305 (M + 18). Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.56; H, 4.63; N, 4.83.

Spirocyclopropane derivative 8b: yield 0.14 g (47%); mp 280 °C (dec, acetone); ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 3H, Me), 1.78 (s, 3H, Me), 2.81 (d, 1H, J = 6.2 Hz), 3.0 (d, 1H, J = 6.2 Hz), 6.9−7.18 (m, 3H, arom), and 7.9 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 21.3, 26.1, 28.3, 41.6, 44.5, 105.8, 111.4, 112.6, 112.9, 117, 123.9, 138.8, 159.5, 162.5, and 171.5; MS (CI/NH_3) m/z 323 (M + 18). Anal. Calcd for $C_{15}H_{12}NO_5F$: C, 59.02; H, 3.96; N, 4.59. Found: C, 58.90; H, 3.97; N, 4.58.

Synthesis of 3-(3-Methylindol-2-on-3-yl)propionic Acid 11. Compound **10** (0.19 g, 1 mmol) was dissolved in t-BuOH (12 mL). t-BuOK (0.05 g, 0.5 mmol) and ethyl acrylate (0.12 mL, 1.1 mmol) were added to the solution at one time, and the reaction mixture was stirred at room temperature under an N_2 atmosphere for 6 h. Then the solvent was removed under reduced pressure, and the residue was dissolved in 90% MeOH/H_2O (15 mL). To this solution was added NaOH (0.2 g, 5 mmol), and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, and the residue was taken up in cold H_2O (15 mL). The solution was cooled and acidified with AcOH. The precipitated solid was filtered, washed with H_2O, and dried. The crude compound was crystallized using MeOH/H_2O: yield 0.14 g (64%); mp 133−35 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 3H, Me), 2.0−2.32 (m, 4H), 6.89 (d, 1H, J = 7.8 Hz, arom), 7.03 (t, 1H, J = 7.8 Hz, arom), 7.13−7.22 (m, 2H, arom), and 8.73 (bs, 1H, NH); ^{13}C NMR (CD_3CN) δ 23.9, 29.9, 33.7, 48.6, 110.7, 123.3, 124.2, 129.1, 134.69, 142.2, 174.8 (CONH-), and 182.6 (COOH); MS (EI) m/z 219. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.84; H, 6.03; N, 6.33.

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