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A Facile Fused-Dioxaza-ring Synthesis from *N*-Hydroxyphthalimide.

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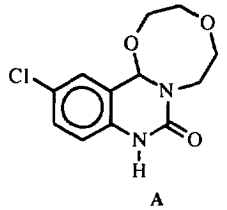
Abstract:

Dioxazino(dioxazepino and dioxazocino)isoindolones **3-5** and isoindolobenzodioxazocine **8** were synthesized from *N*-hydroxyphthalimide by intramolecular nucleophilic substitution of 2-(bromoalkoxy)-3-hydroxyisoindolones **2** and aromatic alcohol-halide **7**.

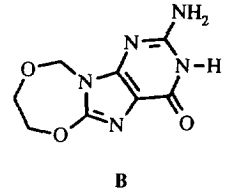
Keywords: *Isoindole - Cyclisation- Polycyclic heterocyclic compounds.*

In the course of synthesis of polyheterocyclic systems, there have been only few attempts to design compounds bearing oxaza or dioxaza moiety. Starting from phthalimide derivatives, some oxazoloisoindoles were synthesized by photochemical cyclization of *N*-o-alkylphenyphthalimides [1] or condensation of *N*-(2-bromoethyl)phthalimide with the dianion of isobutyric acid [2] while oxazinoisoindoles were obtained from 3-(bromobenzylidene) phthalimidin-2-yl acetic acids [3]. Dioxaza derivatives could exhibit interesting pharmacological activity, for example, the dioxazocinoquinazolinone **A** presents uricosuric and antiinflammatory properties [4] and the dioxazepinopurinone **B** shows immunostimulant activity [5] (Scheme 1).

Scheme 1.



A



B

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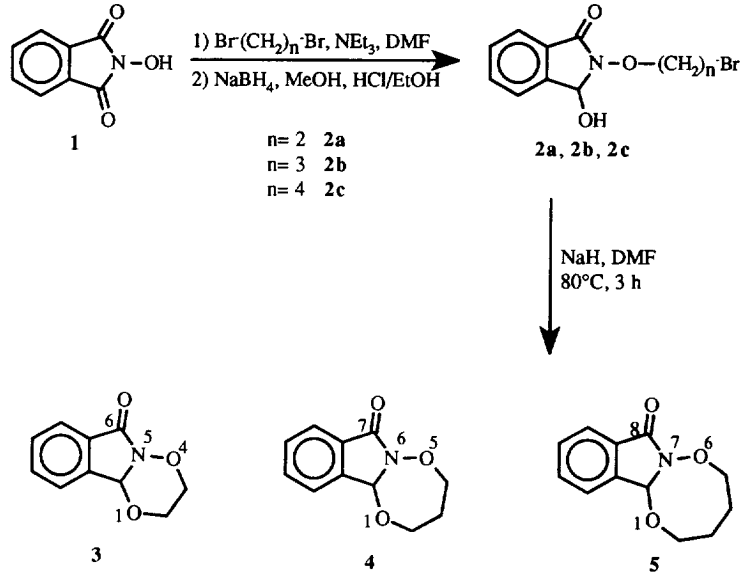
As a part of our studies towards the synthesis of polyheterocycles containing the isoindole group, we have shown that 3-hydroxyindole derivatives could lead easily to thienoindolizino-isoindoles or isoindolobenzodiazepines *via* intramolecular aryl radical cyclization [6,7] and isoindolobenzazepines, thienothiazinoisoindoles or isoindolobenzodiazepines through *N*-acyl-iminium ion cyclization [8-10].

We now wish to report a facile synthesis of dioxazino-, dioxazepino- and dioxazocino-isoindolones starting from commercially available *N*-hydroxyphthalimide **1**. The latter was *O*-alkylated by dibromoalkanes in the presence of triethylamine in DMF at 90°C for 2 hours (Scheme 2).

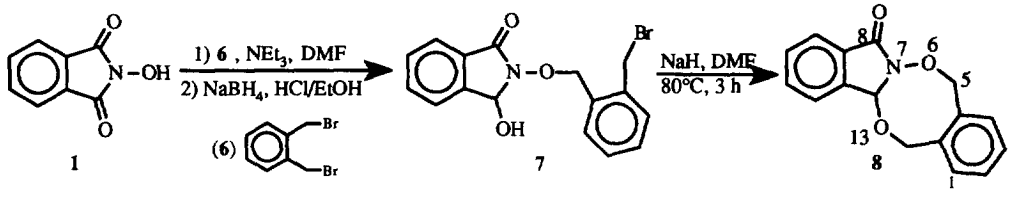
Scheme 2.



Then, the 2-(bromoalkoxy)phthalimides were reduced regioselectively in methanol by sodium borohydride in the presence of acid [11] to corresponding 3-hydroxylactams **2a-c** (40-55% overall yield). Cyclization was performed by heating 3-hydroxyisoindolones **2a-c** in dry DMF in basic conditions using sodium hydride to give 6-,7- and 8- membered dioxaza-ring compounds **3**, **4** and **5**. A direct cyclization of 3-hydroxyisoindolones **2a-c** by heating during several hours the ethanolic reduction medium is possible but this method gave only poor yields.

This versatile method can be extended to the use of aromatic dibromomethyl derivatives. For exemple the α,α'-dibromo-*o*-xylene and **1**, treated under similar conditions as above, led to the isoindolo [2,1-c][1,4,2]benzodioxazocine **8** as depicted on Scheme 3. All the structures of the hydroxylactam intermediates **2a-c**, **7** and final polycyclic isoindolones **3**, **4**, **5** and **8** were supported by their IR, ^{1}H and ^{13}C NMR spectra (200 MHz) as well as by their microanalyses.

Scheme 3.



To our knowledge this is the first example of the synthesis of fused six to eight membered rings containing two oxygens and one nitrogen atom in 1-3-4 position. Further experiments are in progress to synthesize structural analogues.

Procedure and products

General procedure for preparation of cyclic products: To a stirred solution of bromoalkoxyisoindolones **2a-c** or **7** (2.5 mmol) in dry DMF (12 ml) under nitrogen atmosphere was added portionwise sodium hydride (3 mmol) at room temperature over a period of 25 minutes. The reaction mixture was heated at 80°C for 3 hours, then concentrated *in vacuo* and water (5 ml) was added to the residue. After extraction with methylene chloride (3x5 ml), the organic layer was washed with water, dried over magnesium sulfate and evaporated. The remaining oil was purified by column chromatography on silica gel with chloroform-ethanol (99:1) as eluent. Compounds **3** , **4** and **8** were recrystallized from methanol, while **5** was obtained as an oil which crystallized after several days.

Physical data for **3**: yield 84%; mp 142-144°C; IR: 1732 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.89-4.16 (m, 4H, OCH_2CH_2O), 5.99 (s, 1H, H_{10b}), 7.61-7.78 (m, 4H, H arom); ^{13}C NMR ($CDCl_3$): δ 64.1 (C_2), 70.8 (C_3), 81.6 (C_{10b}), 123.4 (C arom), 124.0 (C arom), 129.6 (C_{6a}), 130.5 (C arom), 132.9 (C arom), 139.1 (C_{10a}), 162.7 (CO). Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found : C, 62.71; H, 4.63; N, 7.18.

Physical data for **4**: yield 66%; mp 88-89°C; IR: 1751 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.21 (m, 2H, CH_2), 3.14 (m, 2H, CH_2), 3.73 (m, 2H, CH_2), 6.59 (s, 1H, H_{11b}), 7.54-7.85 (m, 4H, H arom); ^{13}C NMR ($CDCl_3$): δ 29.0 (C_3), 47.69 (C_2), 68.2 (C_4), 96.2 (C_{11b}), 123.8 (C arom), 124.7 (C arom), 126.4 (C_{7a}), 130.3 (C arom), 134.5 (C arom), 145.05 (C_{11a}); 168.8 (CO). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.21; H, 5.36; N, 6.69.

Physical data for **5**: yield 63%; mp 63-66°C; IR: 1755 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.53 (m, 2H, CH_2), 1.73 (m, 2H, CH_2), 2.93 (m, 2H, CH_2), 3.84 (m, 2H, CH_2), 6.18 (s, 1H, H_{12b}), 7.52-7.84 (m, 4H, H arom); ^{13}C NMR ($CDCl_3$): δ 23.2 (C), 23.9 (C), 48.4 (C_2), 70.7 (C_5), 94.8 (C_{12b}), 124.0 (C arom), 124.7 (C arom), 127.1 (C_{8a}), 129.8 (C arom), 133.8 (C arom), 144.1 (C_{12a}), 169.0 (CO). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.53; H, 6.10; N, 6.31.

Physical data for **8**: yield 55%; mp 195°C; IR: 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.77 (d, 1H, H_5, J=12.9 Hz), 5.09 (d, 1H, H_5, J=12.9 Hz), 5.41 (d, 1H, H_{14}, J=14 Hz), 5.52 (d, 1H, H_{14}, J=14 Hz), 5.87 (s, 1H, H_{12b}), 7.18-7.40 (m, 4H, H arom), 7.45-7.77 (m, 4H, H arom); ^{13}C NMR ($CDCl_3$): δ 69.0 (C_{14}), 78.1 (C_5), 87.1 (C_{12b}), 123.3 (C arom), 123.5 (C arom), 128.6 (C arom), 128.7 (C arom), 129.5 (C_{8a}), 129.7 (C arom), 130.0 (C arom), 131.2 (C arom), 132.9 (C arom), 135.0 (C arom), 135.5 (C arom), 138.9 (C_{12a}), 165.4 (CO). Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.73; H, 4.70; N, 5.34.

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