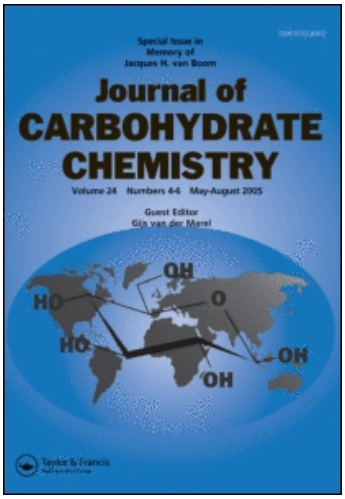

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MAOS of D-Gluconic Acid, D-Glucono-1,4- and 1,5-Lactones, Esters, Hydrazides, and Benzimidazoles Thereof

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MAOS of D-Gluconic Acid, D-Glucono-1,4- and 1,5-Lactones, Esters, Hydrazides, and Benzimidazoles Thereof

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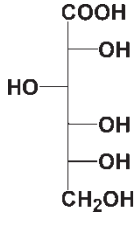
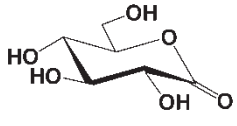
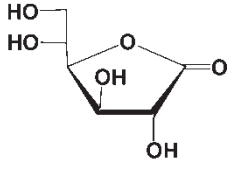
Microwave-assisted organic synthesis (MAOS) of D-gluconic acid can be efficiently done by oxidation of D-glucose with bromine water, upon irradiation with microwave (MW). It was also used for the conversion of D-gluconic acid to ethyl D-gluconate, D-glucono-1,4- and 1,5-lactones, gluconyl hydrazide, and gluconyl phenylhydrazide in yields comparable to those obtained by conventional methods, but in much shorter times. A convenient microwave-mediated condensation of D-gluconic acid with o-phenylenediamines provided the respective acyclonucleoside benzimidazole in short time and good yield.







Keywords Gluconic acid, Gluconolactones, Microwave irradiation, Acyclonucleosides, *C*-Nucleosides, Benzimidazole, Hydrazide

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INTRODUCTION

Carbohydrates have attracted much attention as renewable biomass.[1] Their polyfunctional nature makes them suitable for various transformations into biodegradable and thus environmentally friendly materials. D-Gluconic acid has a wide range of applications; it is involved in a large number of industrial applications,[2,3] including complexing agents, key intermediates for foodstuffs, detergents, textiles, leathers, photographic materials, or pharmaceuticals.[4–6]

On one hand, production of gluconic acid has utilized chemical, electrochemical, and bioelectrochemical approaches.[6–12] On the other hand, biochemical strategies to oxidize glucose into gluconic acid relied on enzymes such as *Aspergillus niger*,[8] *Penicillium sp*.,[9] *Zymomonas mobilis*,[10] and *Gluconobacter oxydans*, or cells.[11–12]

The use of microwave (MW) technology has been reported to cause a dramatic decrease in reaction time and possibly enhance the regio- and stereoselectivities in organic reactions.[13] In line with our desire to develop green chemistry protocols, we applied this technique to our synthetic goals,[14] among which was the preparation of gluconic acid and derivatives.

RESULTS AND DISCUSSION

Oxidation of D-glucose **(1)** with bromine water is one of the oldest and best known reactions in carbohydrate chemistry.[15] Interestingly, microwave irradiation of a mixture of D-glucose, bromine water, calcium carbonate, and calcium chloride in a closed Teflon vessel for 10 min gave D-gluconic acid **(3)** in 83% yield. The conventional method required 24 hours to give a comparable yield.

Alternatively, we have obtained D-gluconic acid from calcium gluconate by reaction with oxalic acid in water under microwave irradiation for 1 min, instead of the 20 min required to get a comparable yield under conventional heating.[16] Since crystallization of D-gluconic acid from complex mixtures is difficult, it is often achieved through its salts or readily crystallizable hydrazides.[17–18] In line with this observation, D-gluconic acid was reacted with hydrazine hydrate or phenylhydrazine in ethanol under MW irradiation for 0.5 to 1.0 min to give the respective hydrazides **7** (80%) and **8** (97%) in crystalline forms, whereas conventional heating required 15 min.

Microwave irradiation of **3** in absolute ethyl alcohol containing a catalytic amount of concentrated hydrochloric acid for 1 min gave ethyl D-gluconate **(4)** in a yield of 66%, far superior to that obtained by conventional heating (25%).[16] Attempted esterification of **3** by methyl alcohol under the same conditions gave D-glucono-1,4-lactone **(5)** in 45% yield instead of the expected ester. Alternatively, **5** could be obtained in 64% yield by irradiation of D-glucono-1,5-lactone (**6**) in acetic acid for 2 min, whereas conventional heating required 2 h to give **6** in 46% yield.[19] On the

other hand, **6** was isolated in quantitative yield upon irradiation of **3** in dioxane for 2 min.

D-Gluconic acid (**3**), the ester **4,** and lactone **6** gave identical hydrazides **7** or **8** upon MW irradiation in the presence of hydrazine or phenyl hydrazine, respectively, for 0.5 to 1.0 min. Furthermore, MW irradiation of hydrazide **7** and *p*-nitrobenzaldehyde in ethanol for 1.5 min gave hydrazone **9** in 90% yield. The conventional synthesis required heating for 2 h to give **9** in a 75% yield. The presence of the *E* and *Z* isomers was apparent in the ^{1}H NMR spectrum of **9,** with two singlets at δ 8.03 and 8.44 ppm corresponding to the HC═N group and two singlets at δ 11.42 and 11.70 ppm corresponding to ═N∼NH, twice in a 4.2:0.8 ratio.

Acyclic polyhydroxyalkyl derivatives of benzimidazole have been prepared by condensation of *o*-phenylenediamines with aldonic acids in 35% to 50% yield after purification by ion-exchange chromatography.[20a] In the present work, syntheses of benzimidazoles **10** and **11** by reaction of **3** with *o*-phenylenediamine and dimethyl-*o*-phenylenediamine, respectively, have been carried out under MW irradiation for 1.5 to 2.0 min. The condensation products **10** and **11** were readily isolated by chromatography postacetylation to give **12** (70%) and **13** (63%) and subsequent quantitative deacetylation.

The structures of acetylated benzimidazoles **12** and **13** were confirmed by ^{1}H NMR spectroscopy, which revealed H-1′ at δ 6.06 ppm (d, $J_{1',2'} = 7.7$ Hz) and δ 5.95 ppm (d, $J_{1',2'} = 8.4$ Hz), respectively. The ^{13}C NMR spectrum of **12** showed C-1′ at δ_C 67.3 ppm and C═N at δ_C 146.7 ppm. The latter was absent in the DEPT spectrum.

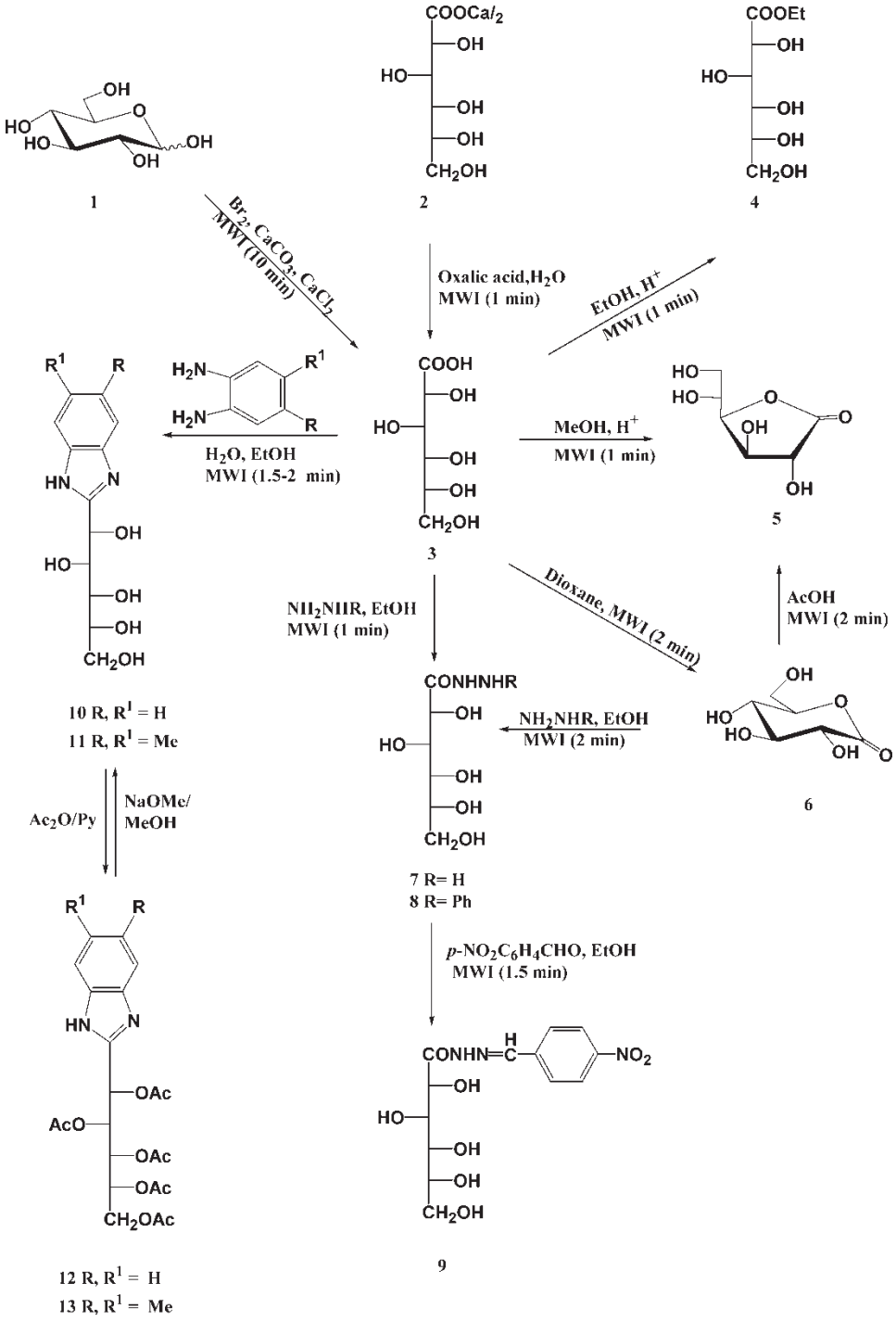
In conclusion, MW irradiation has been successfully employed for the oxidation of D-glucose to D-gluconic acid, a highly desirable industrial intermediate.

Moreover, the technique was also used for converting **3** to esters and 1,4- as well as 1,5-D-gluconolactones, characterized as their hydrazides. An acetylation-deacetylation protocol was used for the isolation of 2-(D-gluco-pentitol-1-yl)benzimidazole, likewise prepared by microwave irradiation, as an acyclonucleoside analog.[21] The shorter reaction times and in some cases the higher yields make the use of this technique a good approach for the clean synthesis of compounds **1**–**13**, thus fulfilling the requirement to develop a "green" method for preparing these compounds, and possibly new analogs (Scheme 1).

EXPERIMENTAL

General Methods

Melting points were determined on a Mel-temp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX



Scheme 1

500 MHz or a Bruker Avance 300 MHz spectrometer. The chemical shifts are expressed on the δ scale using Me_4Si as a standard, and coupling-constant values are given in Hz. The assignments of ^1H NMR spectra were based on chemical-shift correlation DQFCOSY spectra, while the assignment of ^{13}C NMR spectra were based on heteronuclear multiple quantum coherence (HMQC) experiments. TLC was preformed on Merck Silica Gel 60F254; the spots were visualized by charring in sulfuric acid and by UV light. Irradiation was achieved using a domestic microwave oven EM-230 M (800-watt output power). The irradiation was done, unless otherwise stated, in a closed Teflon cylindrical vessel, which was placed at the center of a rotating plate inside the oven. The vessel was supported by a frame for safety. The vessel has an outside diameter 6.5 cm and a length of 6.0 cm, whereas the space inside the vessel was 3.0 cm wide and 2.0 cm long. Moreover, 2.0 cm in the length inside the vessel was used to screw the cover tightly. The oven was adjusted on the defrost mode with the fixed output power. Microanalyses were preformed in the Microanalysis Unit at the Faculty of Science, Cairo University.

D-Gluconic Acid (3)

Method a: In the Teflon vessel, a mixture of D-glucose (0.50 g, 2.78 mmol), calcium chloride (0.05 g, 0.45 mmol), calcium carbonate (0.14 g, 1.40 mmol), and water (10 mL) was treated with bromine (0.5 mL). The closed vessel was irradiated for 10 min. The mixture was allowed to cool and neutralized by calcium carbonate. The filtrate was evaporated until dryness and the residue was extracted with ethanol, which upon evaporation gave **3** as a syrup (0.45 g, 83% yield).

Method b: A mixture of calcium gluconate (15.0 g, 35 mmol), oxalic acid (4.06 g, 45 mmol), and water (2 mL) was placed in an Erlenmeyer flask. This was irradiated for 1.0 min, cooled, and then treated with water (25 mL). The calcium oxalate was removed by filtration and washed with water (5 mL), and the filtrate was evaporated under reduced pressure to give **3** as a syrup (12.5 g, 92% yield).

Ethyl D-Gluconate (4)

A solution of **3** (0.5 g, 2.6 mmol) in absolute ethanol (10 mL) and one drop of concentrated HCl was placed in a closed Teflon vessel and irradiated for 1 min and then cooled. The reaction mixture was triturated with ethanol and the product was recrystallized from ethanol to give colorless crystals (0.38 g, 66% yield); mp. 62–64°C; lit.[16] mp. 62–63°C.

D-Glucono-1,4-lactone (5)

(a) A mixture of **3** (0.25 g, 1.28 mmole), methanol (10 mL), and one drop of concentrated HCl in a closed Teflon vessel was irradiated by microwave for 1.0 min. On cooling the product was separated, which upon recrystallization from ethanol gave colorless crystals (0.10 g, 45% yield); mp. 134–135°C; lit.[19] mp 133–135°C. (b) A solution of D-glucono-1,5-lactone (**6**) (0.25 g, 1.40 mmol) in glacial acetic acid (10 mL) containing one drop of concentrated HCl was placed in a closed Teflon vessel and irradiated for 2 min. The product was washed with glacial acetic acid, ethanol, and ether, then dried to give **5** as colorless crystals (0.16 g, 64% yield); mp. 131–133°C; lit.[19] mp. 133–135°C.

D-Glucono-1,5-lactone (6)

A dry syrup of **3** (1.0 g, 5.2 mmol) was dissolved in dioxane (10 mL) and water (1 mL) and the solution was irradiated for 1.0 min. The reaction mixture was diluted with dioxane (10 mL), irradiated for a further 1.0 min, and cooled, and the solution was nucleated with a crystal of the 1,5-lactone. The product was recrystallized from ethanol (0.83 g, 92% yield); mp. 150–152°C; lit.[19] mp. 150–152°C.

D-Gluconic Acid Hydrazide (7)

A mixture of **3**, **4,** or D-glucono-1,5-lactone (1 mmol), and hydrazine hydrate (0.5 mL) in ethanol (10 mL) was placed in a conical flask where a funnel was placed on its top and then irradiated for 0.5 min. The product was recrystallized from ethanol to give colorless crystals (80% to 85% yield); mp. 144–146°C; lit.[19] mp. 142–144°C; with decomposition at 177–179°C; lit.[19] 176°C.

D-Gluconic Acid Phenylhydrazide (8)

It was prepared as above using phenylhydrazine to give colorless crystals (86% to 97% yield); mp. 203–205°C; lit.[17] mp. 200–202°C.

D-Gluconyl p-Nitrobenzylidene Hydrazide (9)

A mixture of **7** (0.21 g, 1 mmol) and *p*-nitrobenzaldehyde (0.15 g, 1 mmol) in ethanol (10 mL) was irradiated for 1.5 min. The product was recrystallized from ethanol to give **9** as pale yellow crystals (0.27 g, 90% yield); mp. 201–203°C as a 4.2:0.80 mixture of *E* and *Z* isomers; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 3.35 (dd, 1H, $J_{4',3'} = 10.0$ Hz, $J_{4',5'} = 5.4$, H-4′), 3.55 (dd, 1H, $J_{3',2'} = 2.3$ Hz, $J_{3',4'} = 10.0$, H-3′), 3.49–3.44 (under DMSO, 2H, H-5′, H-5″), 3.94 (dd, 1H, $J_{2',1'} = 4.6$, $J_{2',3'} = 2.3$, H-2′), 4.18 (d, 1H, $J_{1',2'} = 4.6$, H-1′), major isomer 7.90 (d, 1.66H, $J_{3,5} = 9.2$, H-2, H-6), 8.26 (d, 1.66, $J_{3,5} = 9.2$,

H-3, H-5), 8.44 (s, 0.83, C*H*═N), 11.42 (s, 0.83, ═N∼N*H*, D_2O-exchangaeble), minor isomer 7.90 (d, 0.34H, $J_{3,5} = 9.2$, H-2, H-6), 8.03 (s, 0.17H, C*H*═N), 8.22 (d, 0.34H, $J_{3,5} = 9.2$, H-3, H-5), 11.70 (s, 0.17H, ═N∼N*H*, D_2O-exchangaeble); ^{13}C NMR ($CDCl_3$) major isomer δ: 63.8 (C-6′), 71.0 (C-2′), 72.0 (C-3′), 72.4 (C-4′), 74.1 (C-5′), 124.6, 128.4, 141.3, 145.5 (Ar-C), 148.3 (H*C*═N), 170.1 (CO), minor isomer δ: 63.8 (C-6′), 70.0 (C-2′), 71.6 (C-3′), 72.3 (C-4′), 73.4 (C-5′), 124.5, 128.4, 141.0, 145.5 (Ar-C), 148.0 (H*C*═N), 174.5 (CO). Anal Calcd. for $C_{13}H_{17}N_3O_8$ (343.10): C, 45.30; H, 4.83; N, 12.18. Found: C, 45.01; H, 5.01; N, 12.47.

2-(1,2,3,4,5-Penta-O-acetyl-D-gluco-pentitol-1-yl)benzimidazole (12)

A mixture of D-gluconic acid (0.50 g, 2.6 mmol) and *o*-phenylenediamine dihydrochloride (1.08 g, 6 mmol) in ethanol (0.1 mL) and water (2 mL) was placed in a closed Teflon vessel and irradiated for 2 min. The dried mixture was suspended in dry pyridine (7 mL), cooled, and then treated with acetic anhydride (10 mL). It was left overnight at rt and then poured into ice water with stirring. The product was extracted with chloroform, washed with water, dried over sodium sulfate, and evaporated. The residue was precipitated by addition of hexane and recrystallized from methanol to give **12** as colorless crystals (0.87 g, 70% yield); mp. 84–86°C. ^1H NMR (300 MHz, $DDCl_3$) δ_H: 1.88, 1.93, 1.95, 1.96, 2.00 (5s, 15H, 5 × CH_3CO), 4.07 (dd, 1H, $J_{5',4'} = 5.5$, $J_{5',5''} = 12.4$, H-5′), 4.20 (dd, 1H, $J_{5'',4'} = 2.8$, $J_{5'',5'} = 12.4$, H-5″), 5.05 (ddd, 1H, $J_{4',3'} = 7.8$, $J_{4',5'} = 5.5$, $J_{4',5''} = 2.8$, H-4′), 5.30 (dd, 1H, $J_{3',2'} = 2.5$, $J_{3',4'} = 7.8$, H-3′), 6.00 (dd, 1H, $J_{1',2'} = 7.7$, $J_{3',2'} = 2.5$, H-2′), 6.06 (d, 1H, $J_{2',1'} = 7.7$, H-1′), 7.52, 7.10 (dd, 4H, Ar-H), 11.9 (s, 1H, NH), ^{13}C NMR ($CDCl_3$) δ: 19.5, 19.5, 19.6, 19.7 (4 × CH_3CO), 60.8 (C-5′), 67.3 (C-1′), 67.6 (C-3′), 67.7 (C-4′), 68.5 (C-2′), 114.7, 122.2, 136.7 (Ar-C), 146.7 (HC═N), 168.5, 168.9, 169.1, 169.3, 169.7 (5 × CH_3CO). Anal Calcd. for $C_{22}H_{26}N_2O_{10}$ (478.45): C, 55.02; H, 5.64; N, 5.73. Found: C, 55.32; H, 5.94; N, 5.95.

5,6-Dimethyl-2-(1,2,3,4,5-penta-O-acetyl-D-gluco-pentitol-1-yl)benzimidazole (13)

This was obtained analogously to compound **12** from **3** (0.50 g, 2.6 mmol) and dimethyl-*o*-phenylenediamine dihydrochloride (1.08 g, 6 mmol). The product was purified using column chromatography to give **13** as colorless crystals (0.83 g, 63% yield); mp. 116–118°C. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.94, 2.04, 2.07, 2.08, 2.09 (5s, 15H, 5 × CH_3CO), 2.31 (s, 6H, 2 × CH_3), 4.04 (dd, 1H, $J_{5',4'} = 5.4$, $J_{5',5''} = 12.2$, H-5′), 4.24 (dd, 1H, $J_{5'',4'} = 3.1$, $J_{5'',5'} = 12.2$, H-5″), 5.13 (ddd, 1H, $J_{4',3'} = 7.6$, $J_{4',5'} = 5.4$, $J_{4',5''} = 3.1$, H-4′), 5.32 (dd, 1H $J_{3',2'} = 2.3$, $J_{3',4'} = 7.6$, H-3′), 5.95 (d, 1H, $J_{2',1'} = 8.4$, H-1′), 6.05 (dd, 1H $J_{2',3'} = 2.3$, $J_{2',1'} = 8.4$, H-2′), 7.2–7.80 (2dd, 2H, Ar-H), 9.92 (s, 1H, NH,

D_2O-exchangeable). Anal Calcd. for $C_{24}H_{30}N_2O_{10}$ (506.19): C, 57.33; H, 6.45; N, 5.25. Found: C, 57.03; H, 6.14; N, 5.55.

2-(D-Gluco-pentitol-1-yl)benzimidazole (10)

A suspension of **12** (1 g, 2.09 mmol) in dry methanol (50 mL) was treated with a solution of sodium methoxide (2 mL; prepared from 0.1 g sodium in 20 mL methanol). The reaction mixture was left overnight at rt and neutralized with ion-exchange resin. The solution was filtered and concentrated under reduced pressure to give a residue that was recrystallized from methanol to give **10** as colorless crystals (0.49 g, 90% yield); mp. 220–221°C, lit.[15] mp. 215–217°C.

2-(D-Gluco-pentitol-1-yl)-5,6-dimethylbenzimidazole (11)

It was obtained, analogously to compound **10**, from compound **13** (1 g, 1.97 mmol) colorless crystals (0.51 g, 90% yield); mp. 204–205°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.24 (s, 6H, 2 × CH_3), 3.25 (dd, 1H, $J_{5',4'} = 7.6$, $J_{5',5''} = 11.5$, H-5′), 3.30 (dd, 1H, $J_{5'',4'} = 5.4$, $J_{5'',5'} = 11.5$, H-5″), 3.49 (ddd, 1H, $J_{4',5'} = 6.1$, $J_{4',5''} = 5.4$, H-4′), 3.96 (d, 1H, $J_{2',1'} = 6.1$, H-2′), 3.57 (under DMSO, H-3′), 4.83 (d, 1H, $J_{2',1'} = 6.9$, H-1′), 7.27, 7.18 (2s, 2H, Ar-H), 11.99 (s, 1H, NH, D_2O-exchangaeble). Anal Calcd. for $C_{14}H_{20}N_2O_5$ (296.32): C, 56.56; H, 6.68; N, 9.79. Found: C, 56.46; H, 6.36; N, 9.48.

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