Synthesis of Indazol-4,7-dione Derivatives as Potential Trypanocidal Agents

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The synthesis of new indazol-4,7-dione derivatives *via* 1,3-dipolar cycloaddition of diazomethane with 2,3-dimethyl-1,4-benzoquinone (**2**) and 1,4-naphthoquinone (**7**) followed by *N*-alkylation of the pyrazol nitrogen atom of the corresponding quinones (**3**) and (**8**) with methyl chloroacetate is described. A series of amides from esters (**5**) and (**10**) were also obtained. These compounds were tested *in vitro* as potential anti-trypanosomal agents. Compounds (**4**) and (**8**) were found to have significant activity.

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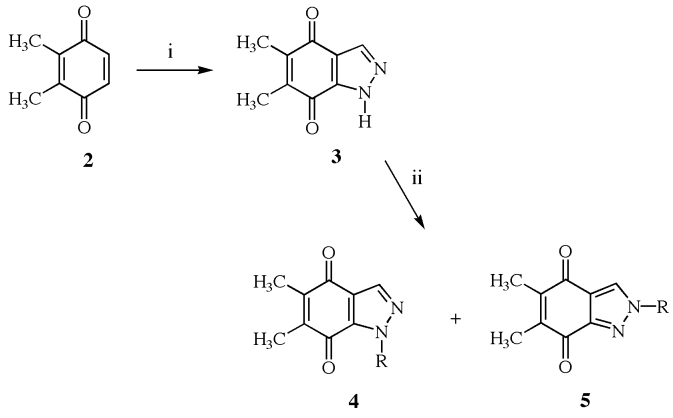
A variety of natural and synthetic compounds containing a *para*-quinone moiety, [1-3] as well as some nitrogen heterocyclic quinones show trypanocidal activity. [4,5]. Chagas'disease, a zoonosis caused by the flagellate protozoan *Trypanosoma cruzi* is of major importance in Central and South America where almost 20% of the population live at risk of infection. [6] Two nitro heterocyclic compounds, nifurtimox and benznidazol, are used for the therapy of acute infections with *Trypanosoma cruzi*. Both have toxic effects and are mutagenic, [7] therefore more effective trypanocidal drugs are needed. In connection with our studies on the preparation of heterocyclic quinones [8-10] we describe here the synthesis of new indazol-4,7-dione derivatives to evaluate its trypanocidal activity.

The synthesis of heterocyclic quinones with the pyrazole ring fused to the quinone moiety was achieved by 1,3-dipolar cycloaddition of diazomethane to quinones [11-13]. This method is useful when the starting quinone is symmetric and it has only one free carbon-carbon double bond, like 2,3-dimethyl-1,4-benzoquinone (**2**). Therefore the synthesis of indazole-4,7-dione (**3**) was attempted by reaction of quinone (**2**) with diazomethane [14]. When this reaction was carried out by treatment of a cold diethyl ether solution of quinone (**2**) with an equimolar amount of diazomethane at 0° C indazole-4,7-dione (**3**) was obtained in 54% yield. Reaction of quinone (**3**) with methyl chloroacetate afforded a mixture of *N*-alkylated derivatives easily isolated by column chromatography. The tautomerism of indazole-4,7-diones has been described in detail and its alkylation reaction usually gave a mixture of *N*-1 and *N*-2 alkylated isomers, so the formation of **4** and **5** was expected [11,15].

Scheme 1



The structural assignment of the *N*-alkylated isomers was performed using ^{1}H nmr NOE difference spectroscopy for each compound. The more polar compound, isolated in 35% yield, was assigned structure **5**, while the less polar isomer was assigned to structure **4**. These assignments are based on the observation that upon irradiation of the methylene and vinyl protons, a larger increase in peak intensities is observed for the more polar compound than that of the less polar compound as shown in Figure 1.

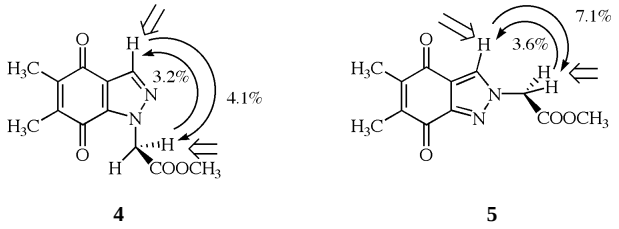
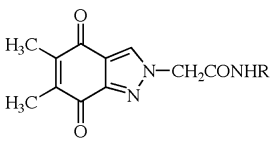


Figure 1. Selected NOE correlations for **4** and **5**.

Next we studied the synthesis of amides using the *N*-alkylated ester (**5**). Reaction of ester (**5**) with 2-aminoethanol, benzylamine and *n*-butylamine at room temperature for 4 hours gave the corresponding amides (**6a-c**).

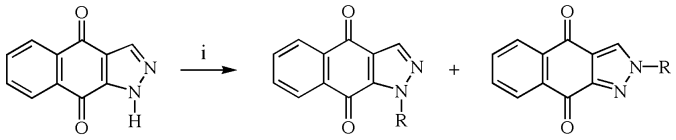


6a R = CH_2CH_2OH
6b R = $CH_2C_6H_5$
6c R = $CH_2CH_2CH_2CH_3$

Preparation of *N*-alkylated derivatives of benzindazol-4,9-diones was studied. With this purpose the heterocyclic quinone (**8**) was synthesized by a modification of the procedure described by Fieser and Peters [16]. The reaction of benzindazol-4,9-dione (**8**) with methyl chloroacetate gave a mixture of two *N*-alkylated products that were isolated by column chromatography.

The structural assignment of the *N*-alkylated isomers (**9**) [17] and (**10**) was confirmed using ^{1}H nmr NOE difference spectroscopy for each compound, and similar result to those of **4** and **5** were obtained. The more polar compound isolated in 39% yield, was assigned structure **10**, and the less polar isomer obtained in 44% yield, structure **9**.

Scheme 2



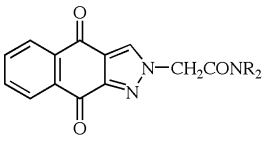
8 **9** **10**

R = CH_2COOCH_3

Reagents: i) $ClCH_2COOCH_3$, K_2CO_3, acetone.

Furthermore the proton chemical shift of the methylene group joined to the heterocyclic nitrogen resonates at higher δ value in compounds **4** and **9** (δ 5.31 and 5.48 ppm respectively) in comparison with those of corresponding isomers **5** and **10** (δ 5.07 and 5.16 ppm respectively). These values are in accord with the structure proposed for compounds **4** and **9** where the methylene group is closer to the quinone carbonyl group.

The reactions of ester **10** with an excess of amine in ethanol at room temperature yielded the corresponding amides **11a-d** (38-92%).



11a R = H, CH_2CH_2OH
11b R = $(CH_2)_5$
11c R = $CH_2CH_2OCH_2CH_2$
11d R = H, $CH_2C_6H_5$

All compounds were screened against *T. Cruzi* epimastigotes Tulahuén strains as described earlier [18,19]. All the amides described herein were shown to be the less active compounds. Nevertheless compounds (**4**) and (**9**) are as active as benznidazol, so we are currently studying the regioselective synthesis of *N*-1 alkylated indazolequinones.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are not corrected. Ir spectra were obtained on a Bruker Model Vector 22 spectrophotometer. Both ^{1}H and ^{13}C nmr spectra were recorded on a Bruker AM-200 spectrometer, using tetramethylsilane as internal reference. Column chromatography separations were performed on Merck silica gel 60 (70-230 mesh). Elemental analyses were carried out on a FISONS EA 1108 CHNS-O analyzer.

2,3-Dimethyl-1,4-benzoquinone (**2**).

To a solution of 100 mg (0.72 mmole) of 2,3-dimethylhydroquinone (**1**) in 10 mL of dry ether was added 500 mg (5.8 mmoles) of manganese dioxide [20] and the mixture was stirred at room temperature for 30 minutes. The inorganic solid was removed by filtration of the reaction mixture through Celite and washed with ether. The combined filtrates were evaporated *in vacuo* and the residue was recrystallized from hexane to give 85 mg (86%) of compound (**2**), mp 54-55 °C (lit.,[21] 55 °C).

5,6-Dimethyl-1*H*-indazole-4,7-dione (**3**).

To a solution of 250 mg (1.84 mmoles) of 2,3-dimethyl-1,4-benzoquinone (**2**) in 30 mL diethyl ether cooled to 0 °C was added drop by drop 25 mL of an ethereal solution of diazomethane 0.07 *M* (1.75 mmoles). After 30 minutes the reaction mixture was filtered to remove some hydroquinone and the filtrate was evaporated *in vacuo*. The residue was recrystallized from methanol to give 175 mg (54%) of compound (**3**), mp 160 °C (decomp). Ir (KBr): 3530 (NH), 1670 (C=O) cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 2.09 (s, 6H, 2xCH_3), 8.10 (s, 1H, H-3), 13.9 (broad s, 1H, NH). ^{13}C nmr (DMSO-d_6): δ 12.1, 12.7, 38.9, 121.5, 136.1, 140.8, 143.4, 178.2, 181.3.

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.10; H, 4.40; N, 15.75.

Methyl (5,6-Dimethyl-4,7-dioxo-4,7-dihydro-1*H*-indazol-1-yl)-acetate (**4**) and Methyl (5,6-Dimethyl-4,7-dioxo-4,7-dihydro-2*H*-indazol-2-yl)-acetate (**5**).

A mixture of 200 mg (1.14 mmoles) of 5,6-dimethyl-1*H*-indazole-4,7-dione (**3**), 140 mg (28.0 mmoles) of methyl chloroacetate and 240 mg (1.74 mmoles) of potassium carbonate in 10 mL of acetone was stirred at 60 °C for 1 hour, followed by stirring 12 hours at room temperature. The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with dichloromethane:ethyl acetate 19:1 to give compounds (**4**) and (**5**).

Compound **4** has mp 129-130 °C (methanol) (30 mg, 11%). Ir (KBr): 1755, 1675, 1660 (C=O) cm^{-1}. ^{1}H nmr ($CDCl_3$): δ 2.08 (s, 6H, 2xCH_3), 3.78 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 7.90 (s, 1H, H-3). ^{13}C nmr ($CDCl_3$): δ 12.0, 12.7, 52.6, 52.9, 121.6, 136.8, 140.7, 143.7, 167.2, 178.1, 181.1.

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.25; H, 5.05; N, 11.35.

Compound **5** has mp 143-144 °C (methanol) (100 mg, 35%). Ir (KBr): 1755, 1675, 1660 (C=O) cm^{-1}. ^{1}H nmr ($CDCl_3$): δ 2.13 (s, 6H, 2xCH_3), 3.81 (s, 3H, CH_3), 5.07 (s, 2H, CH_2), 7.99 (s, 1H, H-3). ^{13}C nmr ($CDCl_3$): δ 12.6, 12.8, 53.1, 53.8, 121.5, 131.3, 143.3, 144.3, 147.5, 166.7, 180.1, 180.7.

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 57.81; H, 4.60; N, 11.02.

N-(Alkyl)-2-(5,6-Dimethyl-4,7-dioxo-4,7-dihydro-2*H*-indazol-2-yl)-acetamides (**6**).

General Procedure.

A mixture of 100 mg (0.40 mmol) of ester (**5**), and 14.0 mmoles of amine was stirred at room temperature for 3 hours. The precipitate was collected by filtration, washed with methanol and dried. Recrystallization from methanol gave the expected compound.

2-(5,6-Dimethyl-4,7-dioxo-4,7-dihydro-2*H*-indazol-2-yl)-*N*-(2'-hydroxyethyl)-acetamide (**6a**).

Compound **6a** has mp 195-196 °C (decomp); (42 mg, 38%). Ir (KBr): 3500 (NH), 1655 (C=O) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.11 (s, 6H, 2xCH_3), 3.20-3.29 (m, 2H, $NHCH_2$), 3.43-3.53 (m, 2H, CH_2OH), 4.86 (t, 1H, *J* =5.3 Hz, OH), 5.09 (s, 2H, NCH_2C=O), 8.45 (broad t, 1H, NH), 8.48 (s, 1H, H-3). ^{13}C nmr ($CDCl_3$): δ 12.2, 12.4, 41.6, 54.6, 59.5, 120.0, 132.7, 142.3, 143.2, 146.3, 165.3, 179.7, 180.2.

Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.20; H, 5.35; N, 15.10.

N-Benzyl-2-(5,6-dimethyl-4,7-dioxo-4,7-dihydro-2*H*-indazole-2-yl)-acetamide (**6b**).

Compound **6b** has mp 220-221 °C (decomp); (46 mg, 36%). Ir (KBr): 3260 (NH), 1670 (C=O) cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.03 (s, 6H, 2xCH_3), 4.40 (d, 2H, *J* =5.9, CH_2Ar), 5.13 (s, 2H, NCH_2C=O), 7.21-7.68 (m, 5H, phenyl), 8.49 (s, 1H, H-3), 8.84 (t, 1H, *J* =5.9, NH). ^{13}C nmr ($CDCl_3$): δ 9.9, 42.3, 47.4, 110.8, 117.6, 126.2, 126.7, 126.9, 127.3, 128.3, 133.3, 138.6, 140.4, 147.5, 165.5, 177.3, 178.1.

Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.75; H, 5.20; N, 12.95.

N-Butyl-2-(5,6-dimethyl-4,7-dioxo-4,7-dihydro-2*H*-indazole-2-yl)acetamide (**6c**).

Compound **6c** has mp 202-203 °C (decomp); (46 mg, 40%). Ir (KBr): 3270 (NH), 1670 (C=O) cm^{-1}. ^1H nmr ($CDCl_3$): δ 0.99 (t, 3H, *J*=7.3 Hz, CH_3), 1.36-1.42 (m, 2H, CH_2), 1.57-1.61 (m, 2H, CH_2), 2.09 (s, 6H, 2xCH_3), 3.20-3.60 (m, 2H, CH_2), 4.99 (s, 2H, NCH_2C=O), 8.45 (s, 1H, H-3), 8.84 (broad t, 1H, NH). ^{13}C nmr ($CDCl_3$): δ 10.2, 13.5, 19.2, 30.9, 32.5, 44.1, 54.4, 109.8, 117.4, 133.2, 147.6, 148.0, 165.2, 177.3, 177.9.

Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.14; H, 6.54; N, 14.46.

1*H*-Benz[*f*]indazol-4,9-dione (**8**).

To a solution of 3.16 g (0.02 mol) of 1,4-naphthoquinone (**7**) in 100 mL diethyl ether cooled to 0 °C was added drop by drop 80 mL of an ethereal solution of diazomethane 0.25 *M* (0.02 mol). After 30 minutes the reaction mixture was filtered the solid thus collected was purified on a silica gel column with dichloromethane. Evaporation of the solvent gave 2.37 g (75%) of compound (**8**), mp >310 °C (lit.,[16] 349 °C). Ir (KBr): 3250 (NH), 1675 (C=O) cm^{-1}. ^1H nmr (DMSO-d_6): δ 7.80-8.35 (m, 4H, H-5, H-6, H-7, H-8), 8.61 (s, 1H, H-3), 14.50 (s, 1H, N-H). ^{13}C nmr (DMSO-d_6): δ 121.5, 126.5, 126.6, 133.7, 134.1; 134.2, 178.9.

Methyl (4,9-Dioxo-4,9-dihydro-1*H*-Benz[*f*]indazole-1-yl)-acetate (**9**) and Methyl (4,9-Dioxo-4,9-dihydro-2*H*-Benz[*f*]indazole-2-yl)-acetate (**10**).

A mixture of 1.56 g (16.0 mmoles) of 1*H*-benz[*f*]indazol-4,9-dione (**8**), 0.96 g (18.0 mmoles) of methyl chloroacetate and 1.63 g (24.0 mmoles) of potassium carbonate in 50 mL of *N*,*N*-dimethylformamide was stirred for 18 hours at room temperature. The mixture was filtered and the filtrate was partitioned in dichloromethane-water. The organic phase was washed with water, dried and evaporated to dryness. Purification by flash column chromatography on silica gel, eluting with dichloromethane: ethyl acetate 3:1 gave compounds (**9**) [21] and (**10**).

Compound **9** has mp 171-172 °C (methanol) (700 mg, 44%). Ir (KBr): 1740, 1675, 1665 (C=O) cm^{-1}. ^1H nmr (DMSO-d_6): δ 3.83 (s, 3H, CH_3), 5.47 (s, 2H, CH_2), 7.70-7.90 (m, 2H, H-6, H-7), 8.13 (s, 1H, H-3), 8.10-8.35 (m, 2H, H-5, H-8). ^{13}C nmr (DMSO-d_6): δ 52.5, 52.8, 122.8, 126.6, 126.7, 132.5, 133.4, 134.1, 134.9, 137.1, 137.6, 167.4, 175.4, 178.5.

Anal. Calcd for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.15; H, 3.66; N, 10.23.

Compound **10** has mp 188-189 °C (methanol) (decomp) (630 mg, 39%). Ir (KBr): 1750, 1690, 1665 (C=O) cm^{-1}. ^1H nmr ($CDCl_3$): δ 3.83 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 7.70-7.90 (m, 2H, H-6, H-7), 8.21 (s, 1H, H-3), 8.18-8.35 (m, 2H, H-5, H-8). ^{13}C nmr ($CDCl_3$): δ 53.3, 54.1, 123.3, 127.3, 127.6, 132.5, 133.9, 134.2, 134.7, 148.4, 166.5, 178.5, 179.1.

Anal. Calcd for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37. Found: C, 61.93; H, 3.48; N, 10.04.

N-(Alkyl)-2-(4,9-dioxo-4,9-dihydro-2*H*-benz[*f*]indazol-2-yl)-acetamides (**11**).

General Procedure.

A mixture of 100 mg (0.37 mmol) of ester (**10**), and 8.0 mmoles of amine in ethanol (10 mL) was heated to reflux stirred for 2 hours. The precipitate was collected by filtration, washed with methanol and dried. Recrystallization from methanol gave the expected compound.

2-(4,9-Dioxo-4,9-dihydro-2*H*-benz[*f*]indazol-2-yl)-*N*-2'-hydroxyethyl)acetamide (**11a**).

Compound **11a** has mp 250-251 °C (decomp); (42 mg, 38%). Ir (KBr): 3435 (OH), 3350 (NH), 1680, 1670 (C=O) cm^{-1}. ^1H nmr (DMSO-d_6): δ 3.20-3.35 (m, 2H, $NHCH_2$), 3.45-3.61(m, 2H, CH_2OH), 4.85 (t, 1H, *J*=5,3 Hz, OH), 5.18 (s, 2H, NCH_2C=O), 7.90-8.05 (m, 2H, H-6, H-7), 8.18-8.30 (m, 2H, H-5, H-8), 8.49 (broad t, 1H, NH), 8.71 (s, 1H, H-3). ^{13}C nmr (DMSO-d_6): δ 41.7, 54.9, 59.5, 121.8, 126.6, 126.8, 133.8, 133.9, 134.1, 134.3, 147.2, 165.2, 177.9, 178.5.

Anal. Calcd for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04. Found: C, 60.34; H, 4.67; N, 13.95.

2-(2-Oxo-2-piperidin-1-yl-ethyl)-2*H*-benz[*f*]indazole-4,9-dione (**11b**).

Compound **11b** has mp 123-124 °C (decomp); (80 mg, 67%). Ir (KBr): 1670 (C=O) cm^{-1}. ^1H nmr ($CDCl_3$): δ 1.50-1.76 (m, 6H, 3x CH_2), 3.40-3.65 (m, 4H, 2x CH_2), 5.22 (s, 2H, NCH_2C=O), 7.70-7.90 (m, 2H, H-6, H-7), 8.24 (s, 1H, H-3), 8.18-8.38 (m, 2H, H-5, H-8). ^{13}C nmr ($CDCl_3$): δ 24.2, 25.3, 26.3, 43.6, 46.4, 54.4, 123.0, 127.3, 127.4, 132.9, 133.7, 134.1, 134.3, 134.8, 148.0, 162.8, 178.7, 179.1.

Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.70; H, 5.25; N, 12.88.

2-(2-Morpholin-4-yl-2-oxo-ethyl)-2*H*-benz[*f*]indazole-4,9-dione (**11c**).

Compound **11c** has mp 268-269 °C; (50 mg, 42%). Ir (KBr): 1685, 1650 (C=O) cm^{-1}. ^1H nmr (DMSO-d_6): δ 3.50-3.85 (m,

8H, 4x CH_2), 5.57 (s, 2H, NCH_2C=O), 7.90-8.05 (m, 2H, H-6, H-7), 8.18-8.32 (m, 2H, H-5, H-8), 8.67 (s, 1H, H-3). ^{13}C nmr (DMSO-d_6): δ 41.9, 44.7, 54.1, 65.8, 121.9, 126.7, 126.8, 134.0, 134.1, 134.3, 147.0, 164.3, 177.9, 178.5.

Anal. Calcd for $C_{17}H_{15}N_3O_4$: C, 62.76; H, 4.65; N, 12.92. Found: C, 63.04; H, 4.75; N, 13.06.

N-Benzyl-2-(4,9-dioxo-4,9-dihydro-2H-benz[f]indazol-2-yl)-acetamide (**11d**).

Compound **11d** has mp 285-286 °C; (120 mg, 92%). Ir (KBr): 3280 (NH), 1690, 1660 (C=O) cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 4.43 (d, *J*=5.8, 2H, CH_2Ar), 5.26 (s, 2H, NCH_2C=O), 7.28-7.52 (m, 5H, phenyl), 7.90-8.05 (m, 2H, H-6, H-7), 8.20-8.32(m, 2H, H-5, H-8), 8.76 (s, 1H, H-3), 8.93 (t, *J*=5.8 Hz, 1H, NH). ^{13}C nmr (DMSO-d_6): δ 42.4, 54.9, 121.8, 126.5, 126.7, 126.9, 127.3, 128.3, 133.8, 133.9, 134.0, 134.3, 138.6, 147.3, 165.2, 177.9, 178.5.

Anal. Calcd for $C_{20}H_{15}N_3O_3$: C, 69.56; H, 4.38; N, 12.17. Found: C, 69.23; H, 4.13; N, 12.03.

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