

## SYNTHESIS OF SOME NEW SPIRO[INDOLINE-3,2'-(1',2',3',4'-TETRAHYDROQUINOLINE)]-2,4'-DIONE DERIVATIVES

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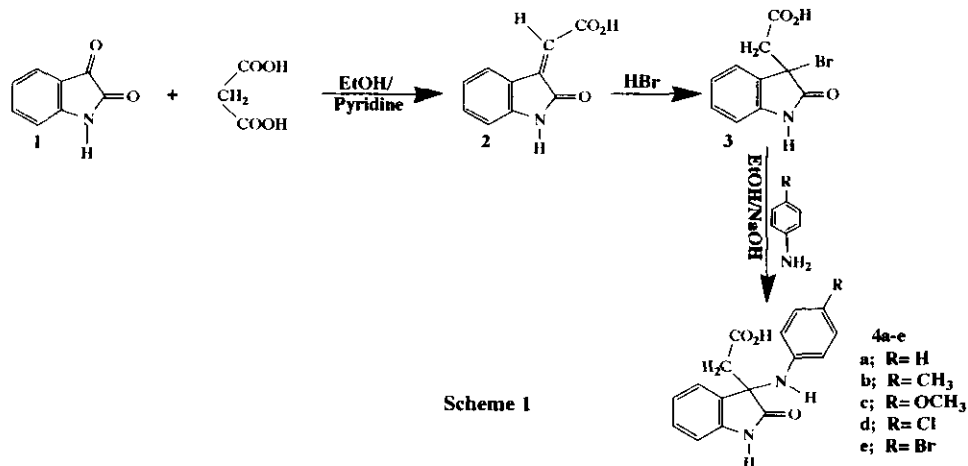
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**Abstract-** Indole-2,3-dione (**1**) was treated with malonic acid in a mixture of ethanol/pyridine to afford 3-(2-oxoindolinylidene)acetic acid (**2**), which then reacted with hydrobromic acid to yield 3-bromo-3-(2-oxoindole)acetic acid (**3**). Compound (**3**) reacted with aromatic amines to yield 3-arylamino-3-(2-oxoindole)acetic acid derivatives (**4a-e**). Cyclization of compounds (**4a-e**) with triflic acid afforded spiro[indoline-3,2'-(1',2',3',4'-tetrahydroquinoline)]-2,4'-dione derivatives (**6a-e**). Alkylation of compounds (**4a-e**) with methyl iodide gave 3-arylmethylamino-2-(1-methyl-2-oxoindole)acetic acid derivatives (**5a-e**). Cyclization of compounds (**5a-e**) with triflic acid yielded spiro[indoline-3,2'-(1',2',3',4'-tetrahydroquinoline)]-1,1'-dimethyl-2,4'-dione derivatives (**7a-e**). Also alkylation of compounds (**6a-e**) with methyl iodide yielded compounds (**7a-e**).

Several authors have reported the synthesis and applications of spirocyclic derivatives.<sup>1-10</sup> Also the synthesis of spirocycles as class III antiarrhythmic agent was done.<sup>11</sup> Synthesis of spiro[3*H*-indole-3,4-(4*H*)pyran]-2-(1*H*)-ones having central nervous system activities was carried out.<sup>12</sup> Spirocycloalkylsubstituted azetidiones were used as hypocholesterolemic agents.<sup>13</sup> Spiro compounds showed photochromic properties.<sup>14</sup> The preparation of fluoran derivatives as coloring agents for recording materials was carried out.<sup>15</sup> Also the preparation of spiroazafuranone derivatives to be used for the treatment of neurodegenerative disorders and as anxiolytics was achieved.<sup>16</sup> Spiro derivatives were used as herbicides, insecticides, acaricides and antivirals.<sup>17</sup> From all of the forgoing facts and as a continuation of our previous works,<sup>18-21</sup> we report herein the synthesis of some new spiro[indoline-3,2'-tetrahydroquinoline]-2,4'-dione derivatives.

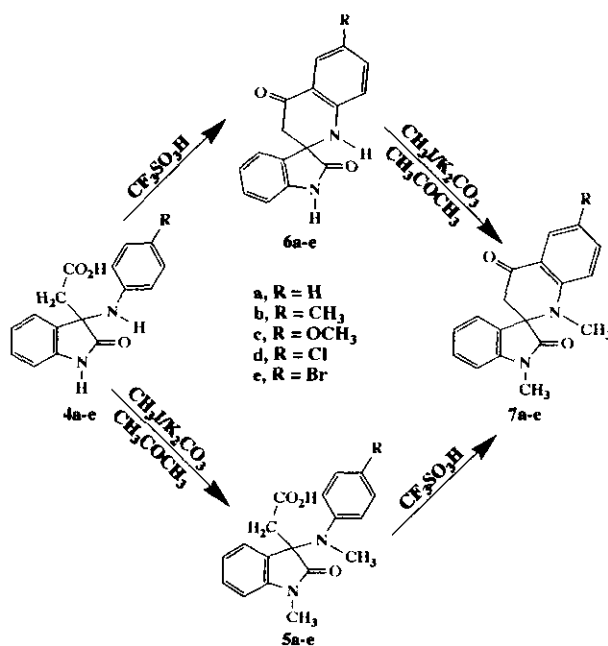
Our syntheses started with the reaction of indole-2,3-dione (**1**) with malonic acid to yield (*Z*) 3-(2-oxoindolinylidene)acetic acid (**2**).<sup>21</sup> Compound (**2**) reacted with hydrobromic acid to afford 3-bromo-3-(2-

oxindole)acetic acid (**3**) in good yield. Compound (**3**) was treated with aromatic amines in alcoholic sodium hydroxide solution to afford 3-arylamino-3-(2-oxindole)acetic acid derivatives (**4a-e**) (Scheme 1).



Scheme 1

Reaction of compounds (**4a-e**) with triflic acid yielded the target cyclodehydration products; spiro[indoline-3,2'-(1',2',3',4'-tetrahydroquinoline)]-2,4'-dione derivatives (**6a-e**) (Scheme 2). Alkylation of compounds (**4a-e**) with methyl iodide and anhydrous potassium carbonate in dry acetone afforded 3-arylmethylamino-3-(1-methyl-2-oxindole)acetic acid derivatives (**5a-e**) in good yield. The reaction of compounds (**5a-e**) with triflic acid yielded spiro[indoline-3,2'-(1',2',3',4'-tetrahydroquinoline)]-1,1'-dimethyl-2,4'-dione derivatives (**7a-e**) in good yields (Scheme 2). For the rigid identification of compounds (**7a-e**), unequivocal syntheses for (**7a-e**) were established by the alkylation of compounds (**6a-e**) with methyl iodide.



Scheme 2

**Table 1.** Physical Data of 3-Arylamino-3-(2-oxoindole)acetic Acid Derivatives (**4a-e**), (**5a-e**) and Spiro[indoline-3,2'-(1',2',3',4'-tetrahydroquinoline)]-2,4'-dione Derivatives (**6a-e**) and (**7a-e**)

Compound No.	Yield (%)	mp (°C)	Molecular Formula (Solvent of Crystallization)	IR (ν, cm <sup>-1</sup> ) (KBr)	NMR (δ, ppm) (DMSO-d <sub>6</sub> )	Anal. Calcd/(Found) %		
						C	H	N
<b>4a</b>	55	285-287	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> (dioxane)	2600-3400 (OH), 3200 (NH), 3000 (CH arom.), 2850 (CH aliph.), 1705, 1725 (C=O)	4.60 (2H, s), 5.10 (1H, s), 5.20 (1H, s), 7.70-8.30 (9H, m), 10.90 (1H, s)	68.08 (68.02)	5.00 (4.94)	9.92 (9.87)
<b>4b</b>	56	290-292	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> (dioxane)	2600-3400 (OH), 3200 (NH), 3050 (CH arom.), 2850 (CH aliph.), 1705, 1720 (C=O)	2.30 (3H, s), 4.60 (2H, s), 5.10 (1H, s), 5.20 (1H, s), 7.70-8.30 (8H, m), 10.90 (1H, s)	68.91 (68.86)	5.44 (5.40)	9.45 (9.41)
<b>4c</b>	58	300-302	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub> (dioxane)	2600-3400 (OH), 3200 (NH), 3060 (CH arom.), 2850 (CH aliph.), 1705, 1725 (C=O)	3.20 (3H, s), 4.60 (2H, s), 5.10 (1H, s), 7.70-8.40 (8H, m), 10.90 (1H, s)	65.38 (65.30)	5.16 (5.09)	8.97 (8.92)
<b>4d</b>	53	295-297	C <sub>16</sub> H <sub>13</sub> N <sub>2</sub> O <sub>3</sub> Cl (dioxane)	2600-3400 (OH), 3180 (NH), 3000 (CH arom.), 2850 (CH aliph.), 1705, 1725 (C=O)	4.60 (2H, s), 5.10 (1H, s), 5.20 (1H, s), 7.60-8.30 (8H, m), 10.90 (1H, s)	60.67 (60-62)	4.14 (4.08)	8.84 (8.80)
<b>4e</b>	52	320-322	C <sub>16</sub> H <sub>13</sub> N <sub>2</sub> O <sub>3</sub> Br (dioxane)	2600-3400 (OH), 3200 (NH), 3050 (CH arom.), 2850 (CH aliph.), 1705, 1725 (C=O)	4.60 (2H, s), 5.10 (1H, s), 5.20 (1H, s), 7.70-8.30 (8H, m), 10.90 (1H, s)	53.21 (53.14)	3.63 (3.57)	7.76 (7.70)
<b>5a</b>	56	290-292	C <sub>18</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> (dioxane)	2600-3400 (OH), 3000 (CH arom.), 2850 (CH aliph.), 1705, 1725 (C=O)	3.25 (3H, s), 3.30 (3H, s), 4.70 (2H, s), 7.70-8.40 (9H, m), 10.90 (1H, s)	69.66 (69.60)	5.85 (5.80)	9.03 (8.96)
<b>5b</b>	55	295-297	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> (dioxane)	2600-3400 (OH), 3050 (CH arom.), 2850 (CH aliph.), 1705, 1725 (C=O)	2.30 (3H, s), 3.25 (3H, s), 3.40 (3H, s), 4.60 (2H, s), 7.75-8.45 (8H, m), 10.90 (1H, s)	70.35 (70.30)	6.21 (6.18)	8.64 (8.58)
<b>5c</b>	57	300-302	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> (dioxane)	2600-3400 (OH), 3060 (CH arom.), 2900 (CH aliph.), 1705, 1725 (C=O)	3.25 (3H, s), 3.30 (3H, s), 3.37 (3H, s), 4.60 (2H, s), 7.75-8.40 (8H, m), 10.90 (1H, s)	67.05 (66.98)	5.92 (5.86)	8.23 (8.18)
<b>5d</b>	53	300-302	C <sub>18</sub> H <sub>17</sub> N <sub>2</sub> O <sub>3</sub> Cl (dioxane)	2600-3400 (OH), 3060 (CH arom.), 2900 (CH aliph.), 1705, 1725 (C=O)	3.25 (3H, s), 3.40 (3H, s), 4.60 (2H, s), 7.75-8.30 (8H, m), 10.90 (1H, s)	62.70 (62.62)	4.97 (4.92)	8.12 (8.04)
<b>5e</b>	50	302-304	C <sub>18</sub> H <sub>17</sub> N <sub>2</sub> O <sub>3</sub> Br (dioxane)	2600-3400 (OH), 3060 (CH arom.), 2900 (CH aliph.), 1705, 1725 (C=O)	3.25 (3H, s), 3.35 (3H, s), 4.60 (2H, s), 7.75-8.30 (8H, m), 10.90 (1H, s)	55.45 (55.40)	4.40 (4.36)	7.20 (7.14)
<b>6a</b>	55	300-302	C <sub>16</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> (dioxane)	3180 (NH), 3060 (CH arom.), 2900 (CH aliph.), 1705, 1720 (C=O)	4.40 (2H, s), 5.15 (1H, s), 5.20 (1H, s), 7.70-8.40 (8H, m)	72.72 (72.68)	4.58 (4.52)	10.60 (10.54)

(Continued)

**Table 1. (Continued) Physical Data of 3-Arylamino-3-(2-oxoindole)acetic Acid Derivatives (4a-e), (5a-e) and Spiro[indoline-3,2'-(1',2',3',4'-tetrahydroquinoline)]-2,4'-dione Derivatives (6a-e) and (7a-e)**

Compound No.	Yield (%)	mp (°C)	Molecular Formula (Solvent of Crystallization)	IR ( $\nu$ , $\text{cm}^{-1}$ ) (KBr)	NMR ( $\delta$ , ppm) (DMSO- $d_6$ )	Anal. Calcd/(Found) %		
						C	H	N
6b	57	310-312	C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> (dioxane)	3200 (NH), 3050 (CH arom.), 2890 (CH aliph.), 1705, 1720 (C=O)	2.20 (3H, s), 4.40 (2H, s), 5.10 (1H, s), 5.20 (1H, s), 7.70-8.30 (7H, m)	73.37 (73.32)	5.07 (5.04)	10.07 (10.02)
6c	53	315-317	C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> (dioxane)	3180 (NH), 3050 (CH arom.), 2900 (CH aliph.), 1700, 1720 (C=O)	3.20 (3H, s), 4.40 (2H, s), 5.10 (1H, s), 5.15 (1H, s), 7.70-8.40 (7H, m)	69.38 (69.32)	4.79 (4.72)	9.52 (9.46)
6d	50	290-292	C <sub>16</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> Cl (dioxane-water) 1:1	3200 (NH), 3050 (CH arom.), 2850 (CH aliph.), 1700, 1725 (C=O)	4.40 (2H, s), 5.10 (1H, s), 5.17 (1H, s), 7.70-8.30 (7H, m)	64.33 (64.28)	3.71 (3.66)	9.38 (9.32)
6e	52	300-302	C <sub>16</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> Br (dioxane-water) 1:1	3180 (NH), 3050 (CH arom.), 2900 (CH aliph.), 1705, 1725 (C=O)	4.45 (2H, s), 5.10 (1H, s), 5.15 (1H, s), 7.75-8.40 (7H, m)	56.00 (55.94)	3.23 (3.18)	8.16 (8.12)
7a	55	310-312	C <sub>18</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> (dioxane-water) 1:1	3060 (CH arom.), 2900 (CH aliph.), 1705, 1720 (C=O)	3.20 (3H, s), 3.25 (3H, s), 4.50 (2H, s), 7.70-8.40 (8H, m)	73.95 (73.92)	5.52 (5.48)	9.58 (9.54)
7b	56	295-297	C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub> (dioxane-water) 1:1	3050 (CH arom.), 2890 (CH aliph.), 1705, 1725 (C=O)	2.20 (3H, s), 3.20 (3H, s), 3.27 (3H, s), 4.50 (2H, s), 7.75-8.50 (7H, m)	74.49 (74.44)	5.92 (5.86)	9.14 (9.08)
7c	58	285-287	C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> (dioxane-water) 1:2	3060 (CH arom.), 2900 (CH aliph.), 1705, 1725 (C=O)	3.15 (3H, s), 3.18 (3H, s), 3.20 (3H, s), 4.50 (2H, s), 7.70-8.50 (7H, m)	70.79 (70.72)	5.63 (5.58)	8.69 (8.62)
7d	56	290-292	C <sub>18</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> (dioxane-water) 1:2	3050 (CH arom.), 2910 (CH aliph.), 1700, 1725 (C=O)	3.30 (3H, s), 3.35 (3H, s), 4.50 (2H, s), 7.75-8.80 (7H, m)	66.16 (66.12)	4.63 (4.58)	8.57 (8.52)
7e	53	300-302	C <sub>18</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> Br (dioxane-water) 1:2	3050 (CH arom.), 2900 (CH aliph.), 1700, 1720 (C=O)	3.25 (3H, s), 3.28 (3H, s), 4.50 (2H, s), 7.75-8.70 (7H, m)	58.24 (58.20)	4.07 (4.02)	7.55 (7.48)

## EXPERIMENTAL

The time required for completion of each reaction was monitored by TLC. Melting points are uncorrected. NMR ( $\delta$ , ppm) spectra were measured on an EM-360 90-MHz spectrometer using TMS as internal standard. IR ( $\nu$ ,  $\text{cm}^{-1}$ ) spectra were recorded on a Pye-Unicam SP 200-G spectrophotometer. Elemental analyses were determined on a Perkin Elmer 240 C microanalyser.

### Preparation of 3-(2-Oxoindolinylidene)acetic Acid (2)

This compound was prepared according to our reported method.<sup>21</sup>

### Preparation of 3-Bromo-3-(2-oxoindole)acetic Acid (3)

Compound (**2**) (18.9 g, 0.1 mol) was treated with concentrated hydrobromic acid (30 mL); the reaction mixture was stirred at rt for 0.5 h whereby the bromo acid was precipitated. It was filtered off, washed with petroleum ether 80-100 °C then crystallized from acetic acid to yield **3** 25 g (93%), mp 320-322 °C, IR ( $\nu$ ,  $\text{cm}^{-1}$ ) (KBr): 2600-3400 (OH), 3200 (NH), 3000 (CH arom.), 2850 (CH aliph.), 1705 and 1725 (C=O); NMR ( $\delta$ , ppm) ( $\text{DMSO-d}_6$ ): 4.50 (2H, s), 5.30 (1H, s), 7.70-8.30 (4H, m), 10.90 (1H, s). *Anal.* Calcd for  $\text{C}_{10}\text{H}_8\text{NO}_3\text{Br}$ : C, 44.47; H, 2.99; N, 5.19. Found: C, 44.42; H, 2.92; N, 5.12.

### 3-Arylamino-3-(2-oxoindole)acetic Acid Derivatives (4a-e)

#### General Procedure:

Each primary aromatic amine (0.01 mol) dissolved in ethanolic sodium hydroxide solution (0.02 mol in 30 mL of EtOH) reacted with the calculated amount of **3**. The reaction mixture was refluxed for 6 h, then the reaction mixture was cooled to rt, acidified with 10% HCl, whereby the target product was precipitated. It was filtered off and crystallized from the proper solvent (Table 1).

### 3-Arylmethylamino-2-(1-methyl-2-oxoindole)acetic Acid Derivatives (5a-e)

#### General Procedure:

Each compound (**4a-e**) (0.01 mol) was treated with the calculated amount of methyl iodide (2.8 g, 0.02 mol) in acetone (50 mL) in the presence of the calculated amount of anhydrous potassium carbonate (4.1 g, 0.03 mol). The reaction mixture was refluxed for 6 h, then cooled to rt and the potassium carbonate was filtered off, washed with acetone. The acetone was removed whereby the target product was precipitated. It was filtered off and crystallized from the proper solvent (Table 1).

### Spiro[indoline-3,2'-(1',2',3',4'-tetrahydroquinoline)]-2,4'-dione Derivatives (6a-e)

#### General Procedure:

Each compound (**4a-e**) (0.001 mol) was treated with the calculated amount of triflic acid (0.15 g, 1.0 mmol), then the reaction mixture was stirred at rt for 1 h. The reaction mixture was poured into  $\text{NaHCO}_3$  dissolved in water (30 mL, 10%), whereby the target spiro derivatives (**6a-e**) were precipitated. The products were filtered off washed with water and crystallized from the proper solvent (Table 1).

### Spiro[indoline-3,2'-(1',2',3',4'-tetrahydroquinoline)]-1,1'-dimethyl-2,4'-dione Derivatives (7a-e)

#### General Procedure:

Each compound (**5a-e**) (0.001 mol) was treated with the calculated amount of triflic acid (0.15 g, 1.0 mmol), then the reaction mixture was stirred at rt for 1 h. The reaction mixture was poured into  $\text{NaHCO}_3$  dissolved

in water (30 mL, 10%), whereby the target spiro derivatives (**7a-e**) were precipitated. The products were filtered off, washed with water and crystallized from the proper solvent (Table 1).

## REFERENCES

1. A. A. Abdel-Hafez, A. M. A. Awad, R. A. Ahmed, and K. M. Hassan, *Afinidad*, 1995, **52**, 59.
2. U. Diefenbach and U. Engelhardt, *Phosphorus, Sulfur and Silicon*, 1992, **65**, 65.
3. A. Wulferding, J. H. Jankowshi, and M. R. Hoffman, *Chem. Ber.*, 1994, **127**, 1275.
4. S. Stverkova, Z. Zak, and J. Jonas, *Liebigs Ann. Chem.*, 1995, **3**, 477.
5. T. V. Lee and J. R. Porter, *Org. Synth.*, 1995, **72**, 189.
6. C. M. R. Ribeiro, S. T. ReMelo, M. Bonin, J. C. Quirion, and H. P. Husson, *Tetrahedron Lett.*, 1994, **35**, 722.
7. S. P. Watson, G. R. Knox, and N. M. Heron, *Tetrahedron Lett.*, 1994, **35**, 9763.
8. L. Fitjer, A. Kanschik, and M. Majewski, *Tetrahedron*, 1994, **50**, 10867.
9. M. S. Malamas, *J. Heterocycl. Chem.*, 1994, **31**, 565.
10. T. Naito, H. Tanada, Y. Suzuki, H. Saito, I. Ninomiya, and T. Kiguchi, *Nat. Prod. Lett.*, 1993, **2**, 309.
11. E. Fanghanel, T. Palmer, J. Kersten, R. Ludwigs, K. Peters, and H.G. Von Schnering, *Synthesis*, 1994, **10**, 1067.
12. R. Jain and M. Bansel, *Pharmazie*, 1995, **50**, 224.
13. S. Dugar, J. W. Clader, D. A. Burnett, M. E. Browne, and H. R. Davis, *PCTInt. Appl. WO 94 17,038* (CL. Co7D205/12), 04 Aug. 1994, US Appl. 6, 439, 21 Jan. 1993, 45 pp., (*Chem. Abstr.*, 1995, **123**, 83220d).
14. K. Tsujita, Y. Suzuki, and A. Myashita, *Jpn. Kokai Tokkyo Koho JP 06,263,767*[94,263,767] (CL. Co 7D 517/10), 20 Sep. 1994, Appl. 93/77,542, 11 Mar. 1993, 7 pp., (*Chem. Abstr.*, 1995, **122**, 105902m).
15. A. Takeda and M. Satomura, *Jpn. Kokai Tokkyo Koho JP 06 ,271,579*[94,271,579] (CL. Co 7D 494/10), 27 Sep. 1994, Appl. 93/60,509, 19 Mar. 1993, 13 pp., (*Chem. Abstr.*, 1995, **122**, 105858b).
16. I. Gacsalyi, Z. Budai, K. Reiter, T. Mezei, G. Blasko, G. Simig, M. Fekete, K. Szemerédi, and A. Egyed, *Eur. Pat. Appl. Ep 623, 616* (CL. Co 7D413/12), 09 Nov. 1994, HU Appl. 93/9, 301, 284, 04 May 1993; 14 pp., (*Chem. Abstr.*, 1995, **122**, 81405y).
17. N. Kolocouris, G. B. Foscolos, A. Kolocouris, P. Marakos, N. Pouli, G. Fytas, and S. Ikeda, E. Declercq, *J. Med. Chem.*, 1994, **37**, 2896.
18. M. S. Al-Thebeiti and M. F. El-Zohry, *Phosphorus, Sulfur and Silicon*, 1994, **88**, 251.
19. M. S. Al-Thebeiti, *Heteroatom Chemistry*, 1994, **5**, 571.
20. M. S. Al-Thebeiti and M. F. El-Zohry, *Heteroatom Chemistry*, 1995, **6**, 567.
21. M. S. Al-Thebeiti and M. F. El-Zohry, *Heterocycles*, 1995, **41**, 2475.