Synthesis of New 1,3-indandione Derivatives

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The paper presents synthesis of new 2-substituted-1,3-indandiones. The synthetised compounds were characterised by spectral analysis.

Keywords: 1,3-indandione, phenoxathine, phthalide, 2-benzylidene-1,3-indandione

Substituted 1,3-indandione derivatives have shown a large applicability during the last three decades in the fields of medicine [1-5], biology [6,7] and agriculture [8].

There are many references related to the biological activity of some 2-substituted indan-1,3-dione derivatives such as their good anticoagulant [9], anti-inflammatory [10], analgezic [11], antibacterial [12] or bronchiadilating [13] activities. Taking into consideration the high frequency of embolism or arterosclerosis related diseases, study of 1,3-indandione derivatives aims at finding new potential biologically active compounds. Recently, compounds containing the indandione moiety were reported as inhibitors of human papilloma virus type 11 [14] or inhibitors of aromatase (indanopiridazined), an enzyme involved in estrogens biosynthesis [15]. Some indanopiridazines have also been tested and reported as inhibitors of monoaminoxidase B, which is an enzyme involved in Alzheimer disease [16].

Moreover, 1,3-indandione derivatives may find uses as dyes having a similar structure to indigo-based dyes as well as intermediates in the manufacture of dyes [17-19].

More recent papers describe new potentially biological active compounds containing the indandione ring which have as intermediates 2-aryliden-1,3-indandiones [20,21].

Taking into account that many of the biologically active compounds derived from 1,3-indandione are 2-substituted derivatives or have as intermediates such derivatives, the present paper focuses on synthesis of such 2-substituted compounds.

Experimental part

All chemicals were obtained from commercial sources and used without any further purification. The melting points were determined in open capillaries using an electrical melting point apparatus and are uncorrected. The IR spectra were recorded on a Fourier Transform electrical melting point apparatus and are uncorrected.

The NMR spectra were recorded on a JEOL Genesis DTGS in KBr pellets in the range 4000-400 cm⁻¹. Lambda 400 (operating at 300 MHz for 1H and 75 MHz for 13C, respectively) in DMSO-d6 or CDCl3, using TMS as internal standard. Mass spectra were performed on a Finigan MAT 90 spectrometer using CI technique; Thin Layer Chromatography was achieved on silicagel plates (Merek) and visualisation was made using iodine vapours or UV light (λ=254 nm).

Lactone of o-hydroxymethyl benzoic acid (phthalide) was synthesized according to Weiss procedure [22].

3-Bromophthalalde was synthesized from 1 g (15 mmoles) of phthalide and 3 g (16.8 mmoles) NBS in 30 mL carbon tetrachloride by heating to reflux for 2 h [23]. The reaction mixture was cooled, filtered and the filtrate was concentrated under reduced pressure. The resulted solid weighs 2.5 g (yield 79%) and was purified by recrystallization from toluene (m.p. 82-83 °C).

(3-Phthalidyl)triphenylphosphonium bromide [23]: a mixture of 2 g (9.4 mmoles) of 3-bromophthalide and 2.45 g (9.4 mmoles) triphenylphosphine in 3 mL of glacial acetic acid was heated at reflux for 2 h. The reaction mixture was allowed to rest at room temperature for 36 h. The resulted crystals were filtered under reduced pressure and washed with ethyl ether (yield 74%); the product was recrystallized from toluene (m.p. 259-260 °C).

2-Formylphenoxathiin [24] was synthesized either according to Rieche-Gross method or starting from 2-bromomethylphenoxathiin and urotropine and hydrolysis under acidic conditions of the urotropinium salt which affords the target compound.

2-Phenoxythiinylacetic acid [25] was synthesized by acid hydrolysis of the corresponding thiomorpholide resulted from a Willgerodt reaction of 2-acetyl-phenoxathiin, as it follows: to 9.3 mmoles of its morpholide, 8.3 mL glacial acetic acid, 1.28 mL of 98% sulfuric water were added and the mixture was heated at reflux for 3 h. The reaction mixture was poured into 15 mL of water and treated with an ammonia solution (under mild heating) until pH = 5.5-6. The solid was filtered off and the filtrate was acidified with sulphuric acid until a white precipitate formed, weighing 1.8 g (yield 83%). The product was recrystallized from a mixture of ethanol/water (m.p. 137-138 °C).

(2-Phenoxathiinyl-10,10-dioxide) acetic acid [26] was synthesised by mild oxidation of 2-phenoxathiinylacetic acid according to the literature: a mixture of 7.36 mmoles of 2-phenoxathiinylacetic acid, 10 mL glacial acetic acid and 6 mL of 30% hydrogen peroxide was heated to reflux for one hour. After cooling, the crystals were filtered and washed with water. The resulted product weighs 1.85 g (yield 87%, m.p. 198-200 °C).

3-(2-Phenoxythiinyliden)phthalide (1)

Method A: To a solution of 0.3 g (1.3 mmoles) of 2-formylphenoxathiin in 1mL acetic anhydride, 0.18 g

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(1.3 mmoles) of phthalide are added. The reaction mixture was heated to reflux for 6 h and allowed to stir at room temperature. After 24 h, 0.05 g (0.5 mmoles) of anhydrous potassium acetate were added and the mixture was heated at reflux for another hour; it was cooled to room temperature when a solid formed which was filtered under reduced pressure and washed with 0.5 mL of ethanol. The solid weights 0.22 g (yield 43%) with R = 0.75 (petroleum ether: dichloromethane : ethyl ether : ethyl acetate 7.5 : 2 : 1 : 0.5 volumes) and is recrystallized from glacial acetic acid to yield yellow crystals (m.p. 209-210°C). Method B. To a solution of 0.24 g (0.5 mmoles) of 3-(2-phthalidyl)triphenylphosphonium bromide in 4 mL dry methylene chloride are added 0.114 g (0.5 mmoles) of 2-formylyphenoxathiin under stirring; 0.7 mL (0.511 g, 5 mmoles) triethylamine are then added dropwise [27] and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was washed with water (3 x 25mL) and dried on CaCl₂. It was filtered and allowed to crystallize at room temperature. The resulted yellow crystals were filtered under reduced pressure and washed with 0.5 mL of ethanol. The product weighs 0.09 g (yield 44%) and was purified by recrystallization from glacial acetic acid.

Method C. 0.15 g (1 mmole) of phthalic anhydride was dissolved in 1 mL of acetic anhydride; to this solution 0.26 g (1 mmole) of 2-phenoxythiinylacetic acid was added under stirring and heating. To this latter solution, 0.25 mL (0.182 g, 1.8 mmoles) of triethylamine was added dropwise [28]. The reaction mixture was allowed to react for 72 h at room temperature; 10 mL of water containing 6 mL concentrated HCl were subsequently added. The resulted yellow-reddish solid is filtered under reduced pressure and washed with 2 mL of water. The product weighs 0.28 g (yield 77%) and is recrystallized from glacial acetic acid.

Method D. 0.52 g (2 mmoles) of 2-phenoxythiinylacetic acid was mixed in a mortar with 0.35 g (2.36 mmoles) of phthalic anhydride. The mixture was transferred into a flask and heated to 130°C when it melts. Then 0.1 g (1 mmole) of anhydrous potassium acetate was added and heating was continued for 90 min, keeping the temperature between 170-180°C. The reaction mixture was cooled to 60-70°C and 3.5 mL of ethanol were added, maintaining the temperature at 70°C. The solid formed during cooling was filtered under reduced pressure, washed with 2 mL of water and dried, yielding 0.34 g (yield 44%). It was recrystallized from glacial acetic acid.

1H-NMR (DMSO-d₆, δ ppm): 8.04 (d, 1H, δ J = 8.1 Hz, H1); 7.93 (d, 1H, δ J = 8.1 Hz, H4); 7.86 (t, 1H, δ J = 7.9 Hz, H2); 7.65 (t, 1H, δ J = 7.9 Hz, H3); 7.61-7.64 (m, 2H, H16, H12); 7.25 (d, 1H, δ J = 8.1 Hz, H24); 7.23 (t, 1H, δ J = 7.9 Hz, H22); 7.16 (d, 1H, δ J = 8.1 Hz, H13); 7.13-7.08 (m, 2H, H21, H23); 6.81 (s, 1H, H10); 6.92-6.98 (m, 3H, H12, H20, H22); 4.16 (s, 1H, H8). 13C-NMR (CDCl₃, δ ppm): 151.2 (C13); 142.5 (C5, C6); 136.1 (C2, C3); 129.3 (C10); 128.1 (C11); 127.7 (C15); 126.9 (C23); 126.7 (C20); 124.6 (C21); 123.8 (C1, C4); 121.1 (C14); 119.5 (C18); 118.2 (C12); 117.7 (C22); 58.7 (C8). IR (KBr, ν cm⁻¹): 3065, 2960, 1727, 1652, 1616, 1587, 1405, 1359, 1267, 1173.

3-(2-Phenoxathiinyl-10,10-dioxide)phthalide (3) was synthesized according to method D. A mixture of 1.16 g (4 mmoles) (2-phenoxathiinyl-10,10-dioxide)acetic acid and 0.7 g (4.72 mmoles) of phthalic anhydride were mixed together in a mortar. The mixture was transferred into a flask and heated to 130°C when it melts. 0.2 g (2 mmoles) of anhydrous potassium acetate was added and heating was continued for 90 min, keeping the temperature between 170-180°C. The reaction mixture was cooled to 70-80°C and 7 mL of ethanol were added. The solid was filtered under reduced pressure, washed with 2 mL of water and dried, yielding 1.12 g (yield 67%); R = 0.38 (petroleum ether: dichloromethane : ethyl ether : ethyl acetate 7.5 : 2 : 1 : 0.5 volumes). It is recrystallized from ethanol (m.p. 173-174°C).

1H-NMR (DMSO-d₆, δ ppm): 8.17-8.22 (m, 2H, H12, H13); 8.1 (d, 1H, δ J = 8.1 Hz, H1); 7.8 (t, 1H, δ J = 7.9 Hz, H2); 7.7 (d, 1H, δ J = 8.1 Hz, H4); 7.6 (t, 1H, δ J = 7.9 Hz, H3); 7.61-7.65 (m, 1H, H16); 7.52 (s, 1H, H10); 7.45-7.55 (m, 4H, H21, H22, H23, H24). 13C-NMR (DMSO-d₆, δ ppm): 172.5 (C9); 168.1 (C7); 150.9 (C14); 149.2 (C18); 136.3 (C12); 135.1 (C5, C6); 135.0 (C2); 132.6 (C11); 132.5 (C1, C4); 130.3 (C24, C22); 125.4 (C23); 124.4 (C15); 123.7 (C19); 123.1 (C16); 122.8 (C3); 119.1 (C13); 118.5 (C21); 41.6 (C10). IR (KBr, v cm⁻¹): 3076, 1727, 1708, 1662, 1587, 1405, 1359, 1261, 1232, 1064. MS (Cl, m/z, %): calc. 376 [M⁺]; found 376 (100, [M⁺]). 2-2-(Phenoxythiinyl-10,10-dioxide)-1,3-indandione (4) was prepared by rearrangement of compound 3, using method I. 0.84 g (2 mmoles) of 3-(2-phenoxathiinyl-10,10-dioxide)phthalide were added to a
solution of MeONa (0.08 g Na in 8.5 mL MeOH). The resulting mixture was heated at reflux for 45 minutes, cooled and filtered off the unreacted solid. 20 mL of water acidified with 2 mL of 6N HCl were added and a light pink precipitate forms (yield 65%): Rf = 0.65 (petroleum ether: dichloromethane: ethyl acetate 7.5 : 2 : 1 :0.5 volumes). The product was recrystallized from glacial acetic acid (m.p. 127-128°C).

1H-NMR (DMSO-d6, δ ppm): 8.09 (d, 1H, J = 8.1 Hz, H12); 8.06 (d, 1H, J = 8.1 Hz, H11); 7.99 (d, 1H, J = 8.1 Hz, H15); 7.85-7.79 (m, 2H, H2, H3); 7.71 (dd, 2H; J = 8.1 Hz, J = 2.0 Hz, H14); 7.75-7.66 (m, 4H, H20, H21, H22, H23); 3.8 (s, 1H, H8). 13C-NMR (CDCl3, δ ppm): 190.2, 189.2 (C7, C9); 150.2, 150.8 (C14, C18); 145.0 (C10); 142.5, 140.0 (C5, C6); 135.2, 135.4 (C2, C3); 135.0 (C12); 130.0, 128.3 (C8, C11); 127.9 (C24); 127.2 (C23); 126.8 (C22); 123.3, 123.2 (C1, C4); 120.5, 118.3 (C15, C19); 118.0 (C13); 117.9 (C21). IR (KBr, ν cm⁻¹): 3075, 2922, 2362, 1723, 1684 , 1556, 1450, 1471, 1400, 1267, 1106, 1086. MS (CI, m/z, %): calc. 296 [M+H]+; found 295 (100, [M-H]+).

2-(Phenoxythiinylidene)-1,3-indandione (5). To a mixture of 2.9 g (20 mmoles) of 1,3-indandione and 3.6 g (20 mmoles) of 3-ethoxy-4-methoxybenzaldehyde, 50 mL of glacial acetic acid were added. The mixture was heated and when it became clear, 10 drops of concentrated hydrogen chloride were added. The mixture was heated for 20 minutes at reflux, then allowed to cool to room temperature. The solid formed was filtered and washed with 15 mL of ethanol. 4.83 g of yellow compound was obtained (yield 75%); Rf = 0.77 (chloroform : methanol : petroleum ether 4 : 1 :2 volumes). It was recrystallized from ethanol to yield yellow crystals with m.p. 182-183°C.

1H-NMR (CDCl3, δ ppm): 8.82 (d, 1H, J = 2.0 Hz, H12); 7.95-7.99 (m, 2H, H1, H4); 7.80 (s, 1H, H10); 7.77-7.79 (m, 2H, H2, H3); 7.70 (dd, 1H, J = 8.1 Hz, J = 2.0 Hz, H14); 6.95 (d, 1H, J = 8.1 Hz, H15); 4.33 (q, 2H, J = 7.1 Hz, CH2O); 3.97 (s, 3H, OCH3); 1.58 (t, 1H, J = 7.1 Hz, CH3). 13C-NMR (CDCl3, δ ppm): 190.8, 189.8 (C7, C9); 154.2 (C12); 148.2 (C13), 147.4 (C10); 139.9, 142.2 (C5, C6); 134.8, 135.0 (C2, C3); 131.2 (C16); 126.3, 126.8 (C11, C12); 123.0 (C1, C4); 116.6 (C12); 110.8 (C15); 64.5 (CH2O); 56.1 (OCH3); 14.7 (CH). IR (KBr, ν cm⁻¹): 1705, 1670, 1610-1620, 1580, 1575, 1490, 1450. MS (CI, m/z, %): calc. 308 [M]+; found 309 (100, [M-H]+).

2-(3-Ethoxy-4-hydroxybenzyliden)-1,3-indandione (6). 0.23 g (1 mmole) of 2-formylphenoxythiin were dissolved in 4 mL anhydrous ethanol, and was added to a solution of 0.146 g (1 mmole) of 1,3-indandione in ethanol. Few drops of piperidine 10% solution in ethanol were added. The mixture was heated for 10 minutes and was neutralized with acetic acid and allowed to cool to room temperature. A red precipitate was formed upon cooling, which was filtered, washed on the filter with ethanol and dried; Rf = 0.83 (petroleum ether: dichloromethane : ethyl ether : ethyl acetate 7.5 : 2 : 1 :0.5 volumes). 0.3 g of pure compound formed (yield 84%), with m.p. 160-161°C. It was recrystallized from ethanol to yield crystals with m.p. 182-183°C.

1H-NMR (CDCl3, δ ppm): 8.41 (d, 1H, J = 2.0 Hz, H16); 8.20 (dd, 1H, J = 2.0 Hz, J = 8.1 Hz, H12); 7.97-8.02 (m, 2H, H1, H4); 7.80-7.82 (m, 2H, H2, H3); 7.73 (s, 1H, H10); 7.15 (d, 1H, J = 2.0 Hz, H24); 7.10 (t, 1H, J = 8.1 Hz, J = 2.0 Hz, H22); 7.06 (d, 1H, J = 8.1 Hz, H13); 7.02 (d, 1H, J = 2.0 Hz, H21); 7.0 (t, 1H, J = 8.1 Hz, J = 2.0 Hz, H23). 13C-NMR (CDCl3, δ ppm): 190.2, 189.2 (C7, C9); 150.2, 150.8 (C14, C18); 145.0 (C10); 142.5, 140.0 (C5, C6); 135.2, 135.4 (C2, C3); 135.0 (C12); 130.0, 128.3 (C8, C11); 127.9 (C24); 127.2 (C23); 126.8 (C22); 123.3, 123.2 (C1, C4); 120.5, 118.3 (C15, C19); 118.0 (C13); 117.9 (C21). IR (KBr, ν cm⁻¹): 3075, 2922, 2362, 1723, 1684 , 1556, 1471, 1407, 1207, 1206, 1086. MS (CI, m/z, %): calc. 356 [M]+; found 356 (100, [M]+).
Taking into consideration that the rearrangement of the intermediate \(1\) (3-(2-phenoxathiinyliden)phthalide) into the derivative \(2\) occurred in good yields, several synthetic methods towards the intermediate \(1\) were tried to be optimised, in order to achieve the best route. These routes are depicted in scheme 2.

Thus, 3-(2-phenoxathiinyliden)-phthalide \((1)\) was synthesized by four different routes. Reaction of 2-formylphenoxathiin in presence of acetic anhydride and potassium acetate yields 3-(2-phenoxathiinyliden)phthalide in 43% yield (method A). Treatment of (3-phthalidyl)triphenylphosphonium bromide with 2-formylphenoxathiin leads to compound \(1\) in 44% yield (method B). The same yield was obtained when treating the phthalic anhydride with 2-phenoxathiinylacetic acid in presence of potassium acetate (method D). For the reaction between the phthalic anhydride and 2-phenoxathiinylacetic acid in presence of acetic anhydride and triethylamine, compound \(1\) is obtained in 77% yield (method C). Among the four synthesis methods of 3-(2-phenoxathiiniliden)phthalide, the best yield is obtained when using method C. In the overall synthesis of the compound \(4\), method D was applied as the synthetic route for the corresponding intermediate \(3\). The phthalic anhydride and (2-phenoxathiinyl-10,10-dioxide)acetic acid in presence of potassium acetate yields 3-(2-phenoxathiinyliden-10,10-dioxide)phthalide \(3\), in 67% yield. This compound was subjected to the rearrangement reaction in presence of sodium methoxide leading to the corresponding compound \(4\) in 63% yield (scheme 1).

The structure of compounds was confirmed by NMR spectroscopy. The chemical shifts for hydrogen and carbon atoms were established on the basis of multiplicity, the magnitude of the coupling constants and by comparison with other heteroaromatic compounds [31, 32]. The \(^1\)H NMR spectrum of the intermediate \(1\) shows the characteristic signal for the ethylenic proton (H10) at 6.81 ppm, while for the oxidised compound (intermediate \(3\)) the same signal appears at 7.52 ppm, probably due to the depletion in electrons of the phenoxathiin ring as a result of the sulphur oxidation. Also, the decrease of the melting point for intermediate \(3\) can be accounted to the same loss of aromaticity. Unlike phthalides, the difference in chemical shifts on the corresponding indandiones cannot be observed for the protons in the position 8, since there is no longer an extended conjugated system.

The infrared spectra of the synthesized compounds show similar bands, as a result of the common moieties. Thus, the spectra show bands specific to stretching vibrations of the C-H aromatic bonds (3050-3080 cm\(^{-1}\)), as well as the characteristic bands of the lactone C=O.
carbonyl bond (1700-1780 cm\(^{-1}\)) for phthalides or the ketone carbonyl bond for the compounds which were subjected to rearrangement (1710-1750 cm\(^{-1}\)). Moreover, the spectra show bands for the C-O and C-S bonds between 1020-1300 cm\(^{-1}\), as well as bands for the deformation vibrations of the C-H aromatic bonds between 400-800 cm\(^{-1}\).

The synthesis of the 2-arylidene-1,3-indandione derivatives is based on the direct condensation between 1,3-indandione and aromatic aldehydes as depicted in scheme 3. They may be used to construct more complex structures having an 1,3-indandione moiety that may possess important pharmacological properties.

**Conclusions**

The paper presents new 1,3-indandione derivatives which may possess pharmacological properties. The compounds were synthesized either by condensation of phthalide with acid derivatives of the phenoxathiin moiety, followed by rearrangement of the intermediates or the direct condensation of the 1,3-indandione with aromatic aldehydes under acid or base catalysis.

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**References**