Synthesis and Biological Evaluation of Substituted Thiophenyl Derivatives of Indane-1, 3-dione

D. GILES*, M. S. PRAKASH, and K. V. RAMSESHU

K. M. College of Pharmacy, Madurai. Tamilnadu, India.

Received 18 January 2007; Accepted 2 March 2007

Abstract: Indane-1, 3-dione (1) synthesized by condensation of diethyl phthalate and ethyl acetate in presence of sodium ethoxide gave sodium salt of ester derivative, which on neutralization in presence of sulphuric acid afford 1. Various thiols where converted to their respective disulphide (3) which on treatment with 1 gave 2-substituted thio phenyl derivatives (4a-g) of 1. The synthesized compounds were characterized on the basis of I.R and H¹NMR. Synthesized compounds (4a-g) were investigated for their anticoagulant, analgesic, anti-inflammatory, antifungal, antibacterial and anticancer activities. Some of the synthesized compounds have shown moderate activities.

Keywords: Indane-1, 3-dione, Diazotisation, Anti cancer, Anti-inflammatory, Antibacterial

Introduction

Indane-1,3-dione¹-³ constitute a unique group of compounds due to its 1,3-dicarbonyl nature, having specific physiochemical property which offers wide scope for studies in problems of theoretical organic chemistry particularly on the basis of tautomerism, dual reactivity. It has a wide range of biological activity covering anticoagulant, bactericidal, fungicidal, neurotropopic etc. Aromatic amines where diazotized⁴ and treated with potassium ethyl xanthathe which was prepared by the reaction of carbon disulphide, ethanol in potassium hydroxide, gave aromatic thiols (2). It was oxidized using potassium ferri cyanide in sodium hydroxide afford disulphide (3) in good yield. Indane-1, 3-dione⁵,⁶ on treatment with 3 using potassium carbonate in dry acetone gave substituted derivatives of indane-1, 3-dione (4a-g).

Experimental

Thin layer chromatography was used to find out the completion of the reaction and purity of the compounds synthesized. Melting points were determined by open end capillary tubes by using thiel’s tube containing liquid paraffin and were uncorrected. IR spectra in KBr were
recorded on a Jasco-410 model FTIR spectrophotometer, \(^1\)H NMR spectra were recorded on Brucker spectrophotometer (300MHz) in CDCl\(_3\) using TMS as an internal standard (chemical shifts are expressed in \(\delta\), ppm). The purity of the compounds were checked on silica gel-G coated plates by using chloroform and ethyl acetate (7:3) as the eluent and observed in UV light. All the synthesized compounds (Scheme 1) gave satisfactory elemental analyses.

\[
\begin{array}{c}
+ \\
\text{K}_2\text{CO}_3 \text{ in dry acetone}
\end{array}
\]

\[
\begin{array}{c}
\text{K}_3(\text{Fe(CN)}_6), \\
\text{Methanol in glacial acetic acid}
\end{array}
\]

\[
\begin{array}{c}
\text{FeCl}_3, \\
\text{K}_2\text{CO}_3 \text{ in dry acetone}
\end{array}
\]

| \(R_1\) | \(R_2\) | \(R_3\) |
|--------|--------|--------|
| CH\(_3\) | H | H |
| H | H | CH\(_3\) |
| H | Cl | H |
| H | H | Cl |
| H | H | OCH\(_3\) |
| H | H | H |

Scheme 1
Synthesis and Biological Evaluation of Indane-1, 3-Dione

General procedure for synthesis of substituted dithiodibenzene (3a-f)

To a stirred solution of substituted thiophenol (0.02 mole) in 10% sodium hydroxide (20 mL) aqueous solution of potassium ferricyanide (6.6 g, 0.02 mol in 50 mL of water) was added slowly. The reaction mixture was kept for 1 h with constant stirring. The separated bis substituted phenyl disulphide was filtered. The product is recrystallised using ethanol.

Synthesis of 1,1'-[dithiobis(methylene)]dibenzene (3g)

Benzyl thiol (2 mL) was dissolved in 1:1 methanol glacial acetic acid (50 mL) allowed to run slowly into a stirred solution of iron III chloride (2 g) in methanol (12 mL) and glacial acid (5 mL). After 15 minutes it was diluted with water (100 mL). The oil that separate milky at first latter solidifies when kept at 0°C recrystallised form methanol.

General procedure for the synthesis of 2-substituted indane-1,3-dione (4a-g)

To a solution of indane-1,3-dione (1.5 g, 0.01 M) in dry acetone (20 mL), anhydrous potassium carbonate (5 g) and synthesized disulphide (3a-g) (0.01 M) were added and the contents of the flask were refluxed for 4 h. The resulting solution was filtered and the residue was washed with acetone (3X25 mL) filtered and concentrated, the residue was treated with ice water and recrystallised from methanol.

2-[(2-Methyl phenyl)thio]-indane-1,3-dione (4a)

Melting point = 201°C, yield = 62%, IR (KBr) 3058 (C-H), 1714 and 1671 (C=O), 1554 (C=C), 1H NMR 7.1 - 7.33 (m, 4 H, ArH), 7.61 - 7.93 (m, 4 H, ArH), 2.4 (s, 3H, CH3) 1.6 (m, 1H, CH). Anal. Calculated for C16H12O2S is C (71.62%), H (4.51%), O (11.93%), and S (11.95%) and found to be C (71.85%), H (4.99%), O (12.08%), and S (12.25%).

2-[(4-Methyl phenyl)thio]-indane-1,3-dione (4b)

Melting point = 211°C, yield = 58%, IR (KBr) 3052 (C-H), 1718 and 1668 (C=O), 1561 (C=C), 1H NMR 7.25 - 7.42 (m, 4 H, ArH), 7.65 - 7.85 (m, 4 H, ArH), 2.2 (s, 3H, CH3) 1.5 (m, 1H, CH). Anal. Calculated for C16H12O2S is C (71.62%), H (4.51%), O (11.93%), and S (11.95%) and found to be C (71.85%), H (4.99%), O (12.08%), and S (12.25%).

2-[(3-Chlorophenyl)thio]-indane-1,3-dione (4c)

Melting point = 157°C, yield = 62%, IR (KBr) 3066 (C-H), 1712 and 1670 (C=O), 1552 (C=C), 1H NMR 7.33 - 7.48 (m, 4 H, ArH), 7.68 - 7.86 (m, 4 H, ArH), 1.5 (m, 1H, CH). Anal. Calculated for C15H9ClO2S is C (62.39%), H (3.14%), Cl (12.28%), O (11.08%), and S (11.11%) and found to be C (63.52%), H (3.52%), Cl (13.11%), O (11.58%), and S (12.01%).

2-[(4-Chlorophenyl)thio]-indane-1,3-dione (4d)

Melting point = 195°C, yield = 66%, IR (KBr) 3079 (C-H), 1749 and 1714 (C=O), 1556 (C=C), 1H NMR 7.36 - 7.49 (m, 4 H, ArH), 7.70 - 7.86 (m, 4 H, ArH), 1.4 (m, 1H, CH). Anal. Calculated for C15H9ClO2S is C (62.39%), H (3.14%), Cl (12.28%), O (11.08%), and S (11.11%) and found to be C (63.45%), H (3.44%), Cl (13.05%), O (11.44%), and S (12.06%).

2-[(4-Methoxyphenyl)thio]-indane-1,3-dione (4e)

Melting point = 191°C, yield = 61%, IR (KBr) 3072 (C-H), 1712 and 1675 (C=O), 1552 (C=C), 1H NMR 6.9 - 7.49 (m, 4 H, ArH), 7.77 - 7.96 (m, 4 H, ArH), 3.7 (s, 3H, CH3) 1.5 (m, 1H, CH). Anal. Calculated for C15H12O2S is C (71.62%), H (4.51%), O (11.93%), and S (11.95%) and found to be C (71.85%), H (4.99%), O (12.08%), and S (12.25%).
1H, CH). Anal. Calculated for C_{16}H_{12}O_3S is C (67.59%), H (4.25%), O (16.88%), and S (11.21%) and found to be C (68.22%), H (4.62%), O (17.22%), and S (12.22%)

2-(Phenylthio)-indane-1,3-dione (4f)

Melting point = 218°C, % yield = 68, IR (KBr) 3066 (C-H), 1714 and 1670 (C=O), 1548 (C=C), ^1H NMR 7.1 - 7.33 (m, 5 H, ArH), 7.51 - 8.02 (m, 4 H, ArH), 1.2 (m, 1H, CH). Anal. Calculated for C_{15}H_{10}O_2S is C (70.84%), H (3.96%), O (12.58%), and S (12.61%) and found to be C (71.51%), H (4.29%), O (12.88%), and S (13.22%)

2-(Benzylthio)-indane-1,3-dione (4g)

Melting point = 177°C, % yield = 66, IR (KBr) 3066 (C-H), 2958 (C-H) 1714 and 1670 (C=O), 1554 (C=C), ^1H NMR 7.5 - 7.8 (m, 5 H, ArH), 7.9 - 8.2 (m, 4 H, ArH), 1.3 (s, 2H, CH2), 1.2 (m, 1H, CH). Anal. Calculated for C_{16}H_{12}O_2S is C (71.62%), H (4.51%), O (11.93%), and S (11.95%) and found to be C (72.12%), H (4.95%), O (12.55%), and S (12.02%)

Results and Discussion

The biological activity of the synthesized compounds is presented in Table 1.

Anticoagulant activity

Indane-1, 3-dione processes mainly used as anticoagulant activity which was carried out for 1, 4a-g using the procedure adopted by Miller. The time required to clot formation was measured among these substitution of methyl (4a, b), Chloro (4c, d) group and hydrogen (4g) in thiophenyl group showed good anticoagulant activity when compared to indane-1, 3-dione

Antibacterial activity

Compounds 1,4a-g were evaluated for In vitro antibacterial activity against S.aureus and P. vulgaris. Most of the compounds exhibited significant activity against S.aureus, which is shown in Table 1. Compounds 4f, 4c, 4d and 4e having phenyl, meta and 4 chloro phenyl and 4 methoxy phenyl group attached to indane-1,3-dione by sulphur processes good activity when compared to other synthesized derivatives. But when compared to standard it is less active.

Antifungal activity

Compounds 1,4a-g were evaluated for antifungal activity against Candida albicans. Most of the compounds exhibited significant activity against Candida albicans. Compound 4f, processes good antifungal activity when compared to other derivatives of indane-1,3-dione.

Analgesic activity

Analgesic activity was carried out for 1,4a-g compound using hot plate method. Jump response was taken as end point. The reaction time after and before administration of drug was calculated. Maximum activity was obtained at 45 minutes. Compounds 4a, 4b, 4c, and 4d processes good analgesic activity when compared with other derivatives. But it is less active than standard.

Anti-inflammatory activity

Anti-inflammatory activity was carried out using carrageenan induced paw oedema in rats using plethysmograph. Maximum activity was obtained as 120 minutes for compounds 4a, 4b, 4f and 4g.
Anti cancer activity

*In vitro* anti cancer studies for 1,4a-g were carried out by short term incubation method using DAL cells. The dead cells were determined by using trypan blue and cell count was done using haemocytometer. Considerable activity was observed for the 4e and 4g.

*In vivo* studies for 1,4a-g were carried out using mice. The DAL cells were introduced into peritoneal cavity of mice for tumour development. The cells were aspirated aseptically from tumour developed mice during log phase and cell count was done using trypan blue exclusion method. Anti cancer activity was not observed for the compounds.

Table 1. Biological activity of the synthesized compounds.

| Compounds                                      | Anticoagulant | Antibacterial | Antifungal | Analgesic | Anti-inflammatory | Antitumour |
|------------------------------------------------|---------------|---------------|------------|-----------|------------------|------------|
| Standard drug                                  | Heparin ***   | Amikacin ***  | Griseofulvin *** | Pentazocin *** | Indomethacin *** | 5-Flurouracil *** |
| Indane-1,3-dione(1)                            | *             | *             | *          | **        | *                | *          |
| 2-[(2-Methyl phenyl)thio]-indane-1,3-dione (4a) | **            | *             | **         | **        | ***              | *          |
| 2-[(4-Methyl phenyl)thio]-indane-1,3-dione (4b) | **            | *             | **         | **        | ***              | *          |
| 2-[(3-Chloro phenyl)thio]-indane-1,3-dione (4c) | **            | **            | **         | **        | *                | *          |
| 2-[(4-Chloro phenyl)thio]-indane-1,3-dione (4d) | **            | **            | **         | **        | *                | *          |
| 2-[(4-Methoxy phenyl)thio]-indane-1,3-dione (4e) | *             | **            | *          | *         | **               | *          |
| 2-(Phenylthio)-indane-1,3-dione (4f)            | **            | *             | ***        | *         | ***              | **         |
| 2-(Benzylthio)-indane-1,3-dione (4g)            | *             | **            | *          | ***       | *                | *          |

* Not significant; ** Significant; *** Highly Significant
Acknowledgments

The authors are thankful to Prof. P Ramesh, School of Chemistry, M K University Madurai for his helpful discussion during the research work.

References

1. Meena S, Shankar D, Ramseshu K V and Giles D, Indian J. Chem., 2006, 45B, 1572-1575.
2. Dubers G, Organic and Physical Chemistry of 1,3-Indane diones and related compounds, 1975, 10, 121-143.
3. Durden J A, Biocidal activity of Indane-1,3-dione and related compounds, 1975, 10, 144-171.
4. Horning Gilman and Blatt, Organic Synthesis, Collective Volume III, 809-811.
5. Furniss B S, Hannaford A J, Rogers V, Smith P W G and Tatchell A R, Vogel’s Text book of Organic Chemistry, 1978, 588, 860.
6. Hilgetag G and Martin A, Preparative Organic Chemistry, 635-636, 732, 795.
7. Miller J L, Clinical diagnosis and management by laboratory methods 765-769, 17th Ed. Saunders Company W B, Philadelphia.
8. Mackie and Mcartney Practical Medical Microbiology, Vol II 13th Ed., 260.
9. Kulkarni S K, Hand book of Experimental Pharmacology, 125,128.
10. Mary K T, Cancer letters, 1994, 81, 53-57.
