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.

sahayagiles@yahoo.com

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 were 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 ^1H NMR. 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, neurotropic etc. Aromatic amines were diazotized⁴ and treated with potassium ethyl xanthate 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-dione^{5, 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, ^1H NMR spectra were recorded on Bruker spectrophotometer (300MHz) in CDCl_3 using TMS as an internal standard (chemical shifts are expressed in δ , 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.

	R_1	R_2	R_3
a	CH_3	H	H
b	H	H	CH_3
c	H	Cl	H
d	H	H	Cl
e	H	H	OCH_3
f	H	H	H

Scheme 1

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

To a stirred solution of substituted thiophenol (0.02mole) in 10% sodium hydroxide (20mL) aqueous solution of potassium ferricyanide (6.6g, 0.02mol in 50mL 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 (2mL) was dissolved in 1:1 methanol in glacial acetic acid (50mL) was allowed to run slowly into a stirred solution of Iron III chloride (**2g**) in methanol (12mL) and glacial acid (5mL). After 15 minutes it was diluted with water (100mL). 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 (1.5g, 0.01M) in dry acetone (20mL), anhydrous potassium carbonate (**5g**) and synthesized disulphide (**3a-g**) (0.01M) 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 (3X25mL) 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 =201⁰C, 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 =211⁰C, 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 (72.05%), H (5.02%), O (12.15%), and S (12.35%)

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

Melting point =157⁰C, 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 =195⁰C, 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 =191⁰C, yield=61%, IR (KBr) 3072 (C-H), 1712 and 1675 (C=O), 1552 (C=C), 1168 (C-O), 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 C₁₆ H₁₂ O₃ S 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 =218⁰C, % 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 C₁₅ H₁₀ O₂ S 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 =177⁰C, % 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 C₁₆ H₁₂ O₂ S 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 Miller⁷. 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 Invitro antibacterial activity⁸ 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 activity⁸ 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 activity⁹ 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-inflammatory⁹ activity was carried out using carriageenan 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 cancer¹⁰ 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 aspired 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	
	<i>In-vitro</i>	<i>In-vitro</i>	<i>In-vitro</i>	<i>In-vitro</i>	<i>In-vitro</i>	<i>In-vitro</i>	<i>In-vivo</i>
Standard drug	Heparin ***	Amikacin ***	Griseofulvin ***	Pentazocin ***	Indomethacin ***	5-Fluorouracil ***	
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 McCartney 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.