Synthesis of Heteroxy Arylsulphide Alkanes and Their Antihistaminic Activity

D.B. SHINDE and M.S. SHINGARE*
Department of Chemistry, Marathwada University
Aurangabad-431 004, India

A series of new substituted heteroxy bromo alkanes and substituted heteroxy arylsulphide alkanes have been prepared. The structures of these compounds were confirmed by spectral and analytical data. The heteroxy arylsulphide alkanes were screened for their antithistaminic activity by guinea pig chopped lung anaphylaxis method.

INTRODUCTION

The sulphur containing heterocyclic compounds have been widely used in various medicaments. Anticancer and antifungal activities have been displayed by a variety of heterocyclic sulphids[1,2]. The clinical utility of various sulphides and sulphones is also firmly established[3]. The pharmacological activities associated with organosulphur compounds, in continuation of our work[4] and observation regarding less attention on the synthesis of sulphur analogs of disodium chromoglycate (DSCG) have prompted to undertake synthesis of substituted heteroxy arylsulphide alkanes. DSCG[5] is found to be useful in asthma treatment when administered by inhalation. It appears to block a step in the chain of events triggered by union of antigens with reaginic antibody which leads to release of spasmogens and other mediator of anaphylactic reaction. Since it is believed that the release of mediator such as histamine, leukotrienes etc. precipitates the broncho construction of asthma and inflammation of allergic attack so the synthesised 1-(substituted heteroxy)-2/3-6-arylsulphide alkanes were screened for antithistaminic activity.

The substituted heteroxy bromo alkanes (1-46, Scheme 1) were synthesised by treating dihaloalkanes (Fluka grade) with substituted hydroxy heterocyclic compounds[6–15]. The bromoalkanes were further treated with substituted thiophenols (Fluka grade) in presence of sodium methoxide to give substituted heteroxy arylsulphide alkanes (47–85, Scheme 1).

EXPERIMENTAL

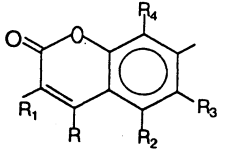
All the melting points were determined in open capillaries using paraffin bath and are uncorrected. IR spectra are recorded on Perkin-Elmer-1420 spectrophotometer in nujol and PMR spectra on FT-80A PMR Spectrophotometer using $CDCl_3$ as solvent and TMS as internal standard. The completion of reaction and purity of synthesised compounds were checked by TLC.

(i) Het–OH + Br–$(CH_2)_n$–Br $\xrightarrow[80°C]{\text{Dry DMF}}$ Het–O–$(CH_2)_n$–Br

(1–46)

(ii) Het–O–$(CH_2)_n$–Br + HS–C$_6$H$_4$–R′ $\xrightarrow{\text{Na–MeOH}}$ Het–O–$(CH_2)_n$–S–C$_6$H$_4$–R′

(47–85)

Het = 

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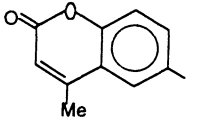
Het = 

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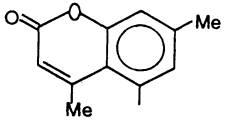
Het = 

III

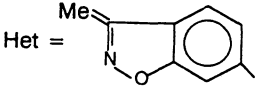
(Ia) R = Me, $R_1 = R_2 = R_3 = R_4$ = H

(Ib) R_2 = Me, $R = R_1 = R_3 = R_4$ = H

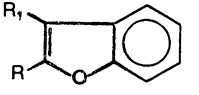
(Ic) R = Me, R_3 = Et, $R_1 = R_2 = R_4$ = H

(Id) $R = R_4$ = Me, $R_1 = R_2 = R_3$ = H

(Ie) R = Me, $R_2 = R_3 = R_4$ = H, R_1 = Cl

Het = 

IV

Het = 

V

R′ = H, 4–Me

n = 2, 3, 4, 5, 6

Va R = H, R_1 = Me

Vb R = COOMe, R_1 = Me

SCHEME 1

1-(4′-Methylcoumarin-7′-oxy)-2-Bromo-Ethane-(1)

The sodium salt of 7-hydroxy-4-methylcoumarin (0.1 mole, 19.8 g) was mixed with 50 ml dry dimethyl formamide (DMF). To this reaction mixture dibromoethane (0.1 mole, 18.8 g) was added in portions with constant stirring. Then the reaction mixture was stirred further for 45 minutes at 80°C. After completion of reaction, the reaction mixture was cooled and poured over crushed ice. The solid obtained was filtered, washed with water and dried. Then it was ether extracted. The ether was removed and solid obtained was crystallised from alcohol to give **1**. Yield 70%, m.pt. 112°C. IR : 1720 (C=O), 1630 (C=C), 1120 and 1260 cm^{-1} (C–O–C); PMR: δ2.4 (s, 3H, γ-pyrone CH_3), 3.51–4.28 (t, 2H, OCH_2–CH_2), 4.24–4.28 (t, 2H, OCH_2–CH_2), 6.06 (s, 1H, β–H to C=O) and 6.60–7.48 (m, 3H, Ar–H).

All other compounds of this series were prepared by the above procedure. Their melting points, yields and analytical data are given in Table 1.

TABLE 1
CHARACTERISATION DATA OF SUBSTITUTED HETEROXYBROMO ALKANES (1–46)

Compd.	Het.	n	Yield (%)	Crystallisation solvent	m.pt. °C	Molecular formula	Found (%) (Calc.)			
							C	H	Br	N
1	Ia	2	70	EtOH	112	$C_{12}H_{11}O_3Br$	51.0 (50.9)	3.8 (3.9)	28.2 (28.3)	—
2	Ia	3	60	EtOH	85	$C_{13}H_{13}O_3Br$	52.4 (52.5)	4.4 (4.4)	26.9 (26.9)	—
3	Ia	4	77	MeOH	65	$C_{14}H_{15}O_3Br$	54.0 (53.9)	4.9 (4.8)	25.8 (25.7)	—
4	Ia	5	65	Pet. ether	60	$C_{15}H_{17}O_3Br$	55.4 (55.3)	5.2 (5.1)	24.7 (24.7)	—
5	Ia	6	76	Pet. ether	79	$C_{16}H_{19}O_3Br$	56.7 (56.8)	5.6 (5.7)	23.6 (23.7)	—
6	Ib	2	72	MeOH	170	$C_{12}H_{11}O_3Br$	51.0 (50.9)	3.8 (3.9)	28.3 (28.3)	—
7	Ib	3	69	EtOH	69	$C_{13}H_{13}O_3Br$	52.4 (52.5)	4.3 (4.4)	26.9 (26.9)	—
8	Ib	4	72	MeOH	89	$C_{14}H_{15}O_3Br$	53.9 (54.0)	4.8 (4.9)	25.6 (25.7)	—
9	Ic	2	75	MeOH	118	$C_{14}H_{15}O_3Br$	53.9 (54.0)	4.8 (4.9)	25.7 (25.7)	—
10	Ic	3	69	EtOH	117	$C_{15}H_{17}O_3Br$	55.3 (55.3)	5.2 (5.1)	24.5 (24.7)	—
11	Ic	4	81	EtOH	85	$C_{16}H_{19}O_3Br$	56.7 (56.8)	5.7 (5.7)	23.6 (23.7)	—
12	Ic	5	73	EtOH	82	$C_{17}H_{21}O_3Br$	57.9 (57.8)	5.8 (5.9)	22.6 (22.7)	—

Compd.	Het.	n	Yield (%)	Crystallisation solvent	m.pt. °C	Molecular formula	Found (%) (Calc.)			
							C	H	Br	N
13	Ic	6	72	EtOH	86	$C_{18}H_{23}O_3Br$	58.8 (58.9)	6.2 (6.3)	21.7 (21.8)	—
14	Id	2	60	MeOH	190	$C_{13}H_{13}O_3Br$	52.4 (52.5)	4.4 (4.4)	26.9 (26.9)	—
15	Id	3	57	EtOH	90	$C_{14}H_{15}O_3Br$	54.0 (53.9)	4.9 (4.8)	25.8 (25.7)	—
16	Id	4	70	MeOH	97	$C_{15}H_{17}O_3Br$	55.4 (55.3)	5.2 (5.1)	24.7 (24.7)	—
17	Id	5	72	EtOH	111	$C_{16}H_{19}O_3Br$	56.7 (56.8)	5.7 (5.7)	23.8 (23.7)	—
18	Id	6	46	MeOH	98	$C_{17}H_{21}O_3Br$	57.9 (57.8)	5.8 (5.9)	23.5 (23.6)	—
19	Ie	2	70	MeOH	131	$C_{12}H_{10}O_3ClBr$	44.1 (44.0)	3.1 (3.0)	24.5 (24.5)	—
20	Ie	3	68	MeOH	112	$C_{13}H_{12}O_3ClBr$	44.3 (44.4)	3.3 (3.4)	22.7 (22.6)	—
21	Ie	4	60	MeOH	115	$C_{14}H_{14}O_3ClBr$	47.2 (47.3)	3.8 (3.9)	22.6 (22.5)	—
22	Ie	5	67	MeOH	131	$C_{15}H_{16}O_3ClBr$	48.9 (48.8)	4.2 (4.3)	21.8 (21.7)	—
23	Ie	6	65	MeOH	57	$C_{16}H_{18}O_3ClBr$	49.9 (50.0)	4.6 (4.7)	20.8 (20.9)	—
24	II	2	67	MeOH	109	$C_{12}H_{11}O_3Br$	50.8 (50.9)	3.8 (3.9)	28.1 (28.3)	—
25	II	3	75	EtOH	87	$C_{13}H_{13}O_3Br$	52.4 (52.5)	4.3 (4.4)	26.9 (26.9)	—
26	II	4	60	EtOH	104	$C_{14}H_{15}O_3Br$	53.9 (54.0)	4.8 (4.9)	25.6 (25.7)	—
27	II	5	60	EtOH	106	$C_{15}H_{17}O_3Br$	55.3 (55.3)	5.2 (5.1)	24.5 (24.7)	—
28	II	6	61	EtOH	90	$C_{16}H_{19}O_3Br$	56.7 (56.8)	5.7 (5.7)	23.6 (23.7)	—
29	III	2	62	EtOH	158	$C_{13}H_{13}O_3Br$	52.4 (52.5)	4.3 (4.4)	26.8 (26.9)	—
30	III	3	72	EtOH	115	$C_{14}H_{15}O_3Br$	53.9 (54.0)	4.9 (4.9)	25.6 (25.7)	—
31	III	4	75	EtOH	119	$C_{15}H_{17}O_3Br$	55.3 (55.3)	5.2 (5.1)	24.5 (24.7)	—
32	III	5	66	EtOH	106	$C_{16}H_{19}O_3Br$	56.6 (56.7)	5.7 (5.6)	23.6 (23.5)	—
33	IV	2	82	MeOH	101	$C_{10}H_{10}O_2NBr$	46.8 (46.9)	3.9 (3.9)	31.3 (31.2)	5.4 (5.5)

Compd.	Het.	n	Yield (%)	Crystallisation solvent	m.pt. °C	Molecular formula	Found (%) (Calc.)			
							C	H	Br	N
34	IV	3	65	Pet. ether	65	$C_{11}H_{12}O_2NBr$	48.8 (48.9)	4.3 (4.4)	29.7 (29.6)	5.1 (5.2)
35	IV	4	47	Pet. ether	64	$C_{12}H_{14}O_2NBr$	50.6 (50.7)	4.8 (4.9)	28.1 (28.2)	4.8 (4.9)
36	IV	5	50	Pet. ether	67	$C_{13}H_{16}O_2NBr$	52.2 (52.3)	5.3 (5.4)	26.7 (26.8)	4.8 (4.7)
37	IV	6	67	Pet. ether	81	$C_{14}H_{18}O_2NBr$	53.7 (53.8)	5.7 (5.8)	25.7 (25.6)	4.4 (4.5)
38	Va	2	62	MeOH	58	$C_{11}H_{11}O_2Br$	49.7 (49.8)	4.2 (4.1)	30.1 (30.2)	—
39	Va	3	51	MeOH	69	$C_{12}H_{13}O_2Br$	51.5 (51.6)	4.5 (4.6)	28.6 (28.7)	—
40	Va	4	69	MeOH	67	$C_{13}H_{15}O_2Br$	53.1 (53.2)	5.0 (5.1)	27.2 (27.3)	—
41	Va	6	67	MeOH	63	$C_{15}H_{19}O_2Br$	56.1 (56.0)	5.8 (5.9)	24.8 (24.9)	—
42	Vb	2	66	EtOH	178	$C_{13}H_{14}O_4Br$	48.2 (48.3)	4.2 (4.3)	25.7 (24.8)	—
43	Vb	3	68	MeOH	90	$C_{14}H_{16}O_4Br$	49.7 (49.8)	4.6 (4.7)	23.6 (23.7)	—
44	Vb	4	57	MeOH	95	$C_{15}H_{17}O_4Br$	51.3 (51.3)	4.9 (4.8)	22.9 (22.8)	—
45	Vb	5	76	MeOH	96	$C_{16}H_{19}O_4Br$	52.5 (52.6)	5.1 (5.2)	21.8 (21.9)	—
46	Vb	6	65	MeOH	57	$C_{17}H_{21}O_4Br$	53.7 (53.8)	5.4 (5.5)	21.0 (21.1)	—

1-(4′-Methyl-6′-ethylcoumarin-7′-oxy)-5-phenylsulphide pentane (55)

Sodium metal (0.1 mole, 2.3 g) was dissolved in dry methanol (100 ml) with external cooling. To this solution thiophenol (0.1 mole, 11 g) was added in portions with constant stirring and cooling. This solution of sodium salt of thiophenol was added to a solution of 1-(4′-methyl-6-ethylcoumarin-7′-oxy)-5-bromo pentane (0.1 mole, 3.53 g) in dry methanol (100 ml) with constant stirring, maintaining temp. below 10°C. The reaction mixture was stirred for 1 hr and refluxed on water bath for 1 h to ensure complete reaction. After completion of reaction, the deposited NaBr was filtered. The filtrate obtained was concentrated and cooled. The solid obtained was filtered, dried and crystallised for methanol to give **55**. Yield 73%, m.pt. 59°C. IR: 1710 (C=O), 1620 (C=C), 1140 and 1260 (C–O–C) and 730 cm^{-1} (C–S); PMR: δ 1.09–1.33 (t, 3H, $-CH_2-CH_3$), 1.55–2.00 (m, 6H, $-(CH_2)_3-$), 2.29 (s, 3H, γ-pyrone CH_3), 2.50–2.73 (q, 2H, CH_2-CH_3), 2.85–3.02 (t, 2H, $-SCH_2-CH_2-$), 3.92–4.07 (t, 2H, $-OCH_2-CH_2-$), 6.06 (s, 1H, β–H to C=O) and 6.73–7.35 (m, 7H, Ar–H).

All other compounds of this series were prepared by the above procedure. Their melting points, yield and analytical data are given in Table 2.

TABLE 2
CHARACTERISATION DATA OF SUBSTITUTED HETEROXY ARYLSULPHIDE ALKANES (47–85)

Compd.	Het.	n	R	Yield (%)	M.pt. °C	Molecular formula	Found (%) (Calc.)			
							C	H	S	N
47	Ia	2	H	89	65	$C_{18}H_{16}O_3S$	69.1 (69.2)	5.0 (5.1)	10.1 (10.2)	—
48	Ia	4	H	86	87	$C_{20}H_{20}O_3S$	70.7 (70.6)	5.8 (5.9)	9.3 (9 4)	—
49	Ia	5	H	77	66	$C_{21}H_{22}O_3S$	71.1 (71.2)	6.2 (6.2)	9.1 (9.0)	—
50	Ia	6	H	90	64	$C_{22}H_{24}O_3S$	71.6 (71.7)	6.4 (6.5)	8.6 (8.7)	—
51	Ib	2	H	90	59	$C_{18}H_{16}O_3S$	69.1 (69.2)	5.0 (5.1)	10.1 (10.2)	—
52	Ic	2	H	90	56	$C_{20}H_{20}O_3S$	70.7 (70.6)	5.8 (5.9)	9.3 (9.4)	—
53	Ic	3	H	73	87	$C_{21}H_{22}O_3S$	71.1 (71.2)	6.1 (6.2)	9.1 (9.0)	—
54	Ic	4	H	89	70	$C_{22}H_{24}O_3S$	71.6 (71.7)	6.4 (6.5)	8.6 (8.7)	—
55	Ic	5	H	73	59	$C_{23}H_{26}O_3S$	72.1 (72.2)	6.7 (6.8)	8.3 (8.4)	—
56	Ic	6	H	90	121	$C_{24}H_{28}O_3S$	72.6 (72.7)	7.1 (7.0)	8.1 (8.0)	—
57	Id	2	H	92	124	$C_{19}H_{18}O_3S$	69.8 (69.9)	5.4 (5.5)	9.7 (9.8)	—
58	Id	3	H	83	105	$C_{20}H_{20}O_3S$	70.7 (70.6)	5.8 (5.9)	9.3 (9.4)	—
59	Id	4	H	90	90	$C_{21}H_{22}O_3S$	71.1 (71.2)	6.1 (6.2)	9.1 (9.0)	—
60	Id	5	H	79	86	$C_{22}H_{24}O_3S$	71.6 (71.7)	6.4 (6.5)	8.6 (8.7)	—
61	Id	6	H	98	105	$C_{23}H_{26}O_3S$	72.1 (72.2)	6.7 (6.8)	8.3 (8.4)	—
62	Ie	2	H	96	70	$C_{18}H_{15}O_3SCl$	62.3 (62.4)	4.4 (4.3)	9.1 (9.2)	—
63	Ie	3	H	75	60	$C_{19}H_{17}O_3SCl$	63.2 (63.3)	4.6 (4.7)	8.7 (8.8)	—
64	Ie	4	CH_3	91	81	$C_{21}H_{21}O_3SCl$	64.8 (64.9)	5.3 (5.4)	8.1 (8.2)	—
65	Ie	5	CH_3	77	98	$C_{22}H_{23}O_3SCl$	65.6 (65.7)	5.6 (5.7)	7.9 (8.0)	—

Compd.	Het.	n	R	Yield (%)	M.pt. °C	Molecular formula	Found (%) (Calc.)			
							C	H	S	N
66	Ie	6	CH_3	74	78	$C_{23}H_{25}O_3SCl$	66.2 (66.3)	6.1 (6.0)	7.7 (7.6)	—
67	II	2	H	83	160	$C_{18}H_{16}O_3S$	69.1 (69.2)	5.0 (5.1)	10.1 (10.2)	—
68	II	3	H	72	101	$C_{19}H_{18}O_3S$	69.8 (69.9)	5.4 (5.5)	9.7 (9.8)	—
69	II	5	H	74	140	$C_{21}H_{22}O_3S$	71.1 (71.2)	6.1 (6.2)	9.1 (9.0)	—
70	II	6	H	89	104	$C_{22}H_{24}O_3S$	71.6 (71.7)	6.4 (6.5)	8.6 (8.7)	—
71	III	2	H	72	120	$C_{19}H_{18}O_3S$	69.8 (69.9)	5.4 (5.5)	9.9 (9.8)	—
72	III	4	H	93	81	$C_{21}H_{22}O_3S$	71.1 (71.2)	6.1 (6.2)	9.1 (9.0)	—
73	III	5	H	79	105	$C_{22}H_{24}O_3S$	71.6 (71.7)	6.4 (6.5)	8.6 (8.7)	—
74	IV	2	H	86	114	$C_{16}H_{15}O_2SN$	67.3 (67.4)	5.2 (5.3)	11.1 (11.2)	4.8 (4.9)
75	IV	3	H	79	80	$C_{17}H_{17}O_2SN$	68.1 (68.2)	5.6 (5.7)	10.6 (10.7)	4.8 (4.7)
76	IV	4	H	90	95	$C_{18}H_{19}O_2SN$	69.1 (69.0)	6.1 (6.0)	10.1 (10.2)	4.4 (4.5)
77	IV	5	H	72	105	$C_{19}H_{21}O_2SN$	69.6 (69.7)	6.3 (6.4)	9.7 (9.8)	4.2 (4.3)
78	IV	6	H	96	100	$C_{20}H_{23}O_2SN$	70.3 (70.4)	6.6 (6.7)	9.3 (9.4)	4.0 (4.1)
79	Va	2	H	86	81	$C_{17}H_{16}O_2S$	71.7 (71.8)	5.7 (5.6)	11.2 (11.3)	—
80	Va	3	H	95	86	$C_{18}H_{18}O_2S$	72.4 (72.5)	6.0 (6.0)	10.6 (10.7)	—
81	Va	4	CH_3	81	79	$C_{20}H_{22}O_2S$	73.5 (73.6)	6.6 (6.7)	9.7 (9.8)	—
82	Va	6	CH_3	75	75	$C_{22}H_{26}O_2S$	54.4 (54.5)	7.2 (7.3)	9.1 (9.0)	—
83	Vb	2	H	93	130	$C_{19}H_{18}O_4S$	66.4 (66.5)	5.6 (5.5)	9.2 (9.3)	—
84	Vb	4	CH_3	94	213	$C_{22}H_{24}O_4S$	68.6 (68.7)	6.1 (6.2)	8.2 (8.3)	—
85	Vb	6	CH_3	85	119	$C_{24}H_{28}O_4S$	69.8 (69.9)	6.7 (6.8)	7.7 (7.8)	—

All compounds were crystallised from methanol.

Pharmacological activity

The pharmacological screening of substituted heteroxy arylsulphide alkanes was carried out in guinea pig at 10 μg/ml concentration. The histamine release

was measured by guinea pig chopped lung anaphylaxis method. During the testing of compound, DSCG was used as reference compound. If the compound produced at least 50% inhibition of release of histamine, it was considered active. The substituted heteroxy arylsulphide alkanes were found to be active at high concentration and less active at minimum concentration.

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