SYNTHETIC USES OF 1-[(METHYLTHIO)THIOCARBONYLMETHYL] PYRIDINIUM IODIDE. SYNTHESIS OF NEW BENZIMIDAZOLE DERIVATIVES.

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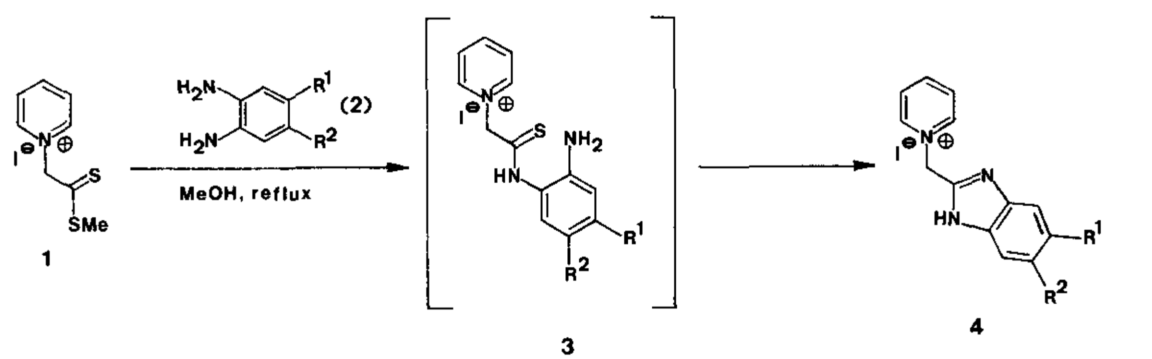
Abstract- Reaction of 1-[(methylthio)thiocarbonylmethyl] pyridinium iodide with substituted o-phenylenediamines gave 1-[(2'-benzimidazolyl)methyl] pyridinium salts which were acylated and mono- and dialkylated by standard procedures. In addition, 2-(1'-piperidinylmethyl)benzimidazole derivatives were prepared by reduction of pyridinium moiety with sodium dithionite.

Benzimidazole derivatives collectively display a wide range of biocidal activities, being used as antihelmintics,[1,2] antitumour agents[3,4] and most importantly as fungicides.[5] Consequently a massive research effort has been expended upon its chemistry with particular emphasis on the synthesis of new derivatives for pharmacological screening.

In connection with our interest in the chemistry of pyridinium ylides[6-8] and as part of a research program focussed on the synthesis of potentially antibacterial compounds,[9-11] we wish to report here the preparation of some 1-[(2'-benzimidazolyl)methyl]pyridinium salts **4** and the subsequent conversion into derivatives **5-9** by simple procedures.

The starting material, 1-[(methylthio)thiocarbonylmethyl] pyridinium iodide **1** was prepared following an already described procedure[12] from 1-phenacylpyridinium iodide. On treatment of **1** with o-phenylenediamines **2** the desired benzimidazoles **4** were obtained in good yield:



Strong electron-withdrawing substituents on benzene ring prevented the cyclization of thioamide intermediates thus, the attempted cyclization of 1-[(2'-amino-5'-nitrophenylamino)thiocarbonylmethyl]-pyridinium iodide **3f** isolated from the reaction of **1** and 1,2-diamino-4-nitrobenzene failed upon diferrent conditions. It was also observed that the benzimidazole **4e** extensively decomposes upon recrystallization from ethanol and no satisfactory microanalysis could be obtained for it.

It should be noted that compound **4a** has been previously obtained in 65 % yield by quaternisation of pyridine with 2-(chloromethyl)benzimidazole[13] but the chloromethyl derivative is obtained in low yield (38 %)[14-16] and its synthesis is difficult to adapt to substituted o-phenylenediamines.

The majority of the compounds described in this paper were prepared from **4a** by methods below indicated. Thus, the first group of reactions afforded alkylated and acylated derivatives **5** and **7**. The alkylation was carried out in acetone[17] under weakly basic conditions. ^{1}H-N.M.R. revealed that alkylation proceeds selectively onto nitrogen either with methyl iodide or benzyl chloride. In contrast, the benzimidazole derivative **8** was the sole product isolated from the reaction of **4a** with carbon disulphide and methyl iodide.[18] The dialkylated derivative **6** was obtained from the reaction of monoalkylated derivative **5a** with benzyl chloride in the reaction system potassium carbonate-acetonitrile.

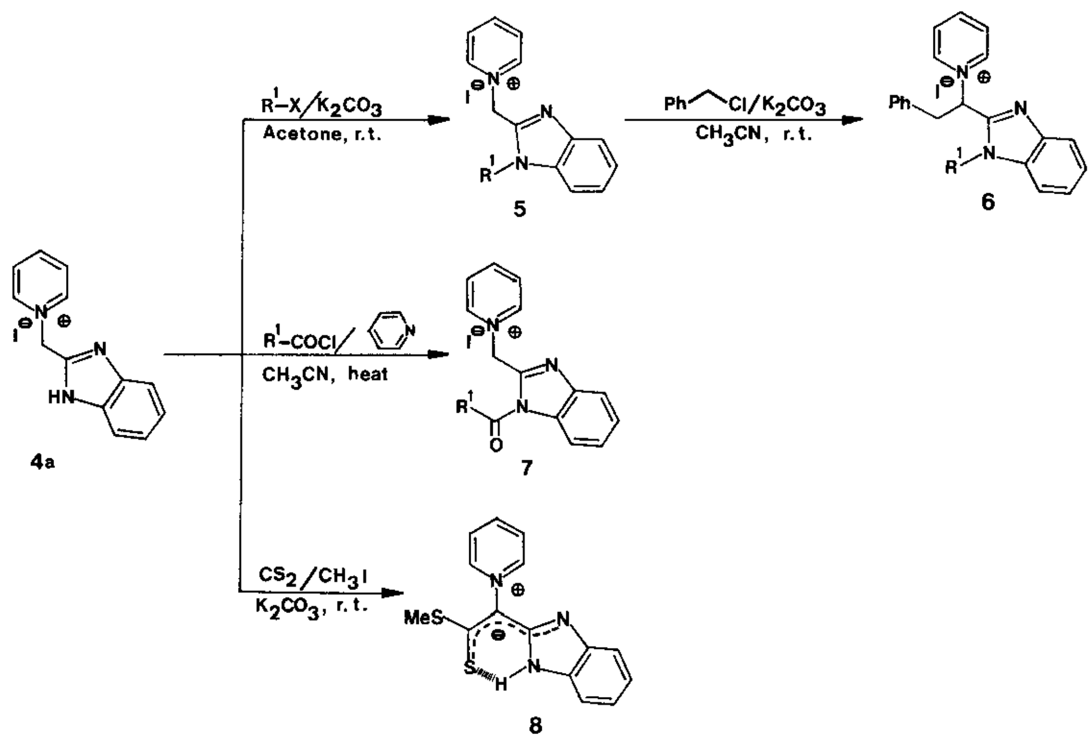


Table. Benzimidazole derivatives **4, 5, 7** and **10** prepared

Product No.	R^1	R^2	Yield (%)	m.p. (°C) (solvent)	Molecular formula[a]	IR (KBr) ν (cm^{-1})	^1H-NMR[b] δ (ppm)
4a	H	H	66	198–199 (EtOH)	$C_{13}H_{12}IN_3$ (337.2)	3200–3100,1630,1585,1540, 1485,1430,1270,1200	6.23(s, 2H); 7.1–7.6(m, 4H); 8.1–9.2(m,5H), 12.76(br, 1H)
4b	H	CH_3	65	178–179 (EtOH)	$C_{14}H_{14}IN_3$ (351.2)	3180–3000,1635,1590,1525, 1480,1210	2.38(s, 3H); 6.15(s, 2H); 6.8–7.5(m, 3H); 8.1–9.2(m, 5H); 12.60(br, 1H)
4c	H	Cl	76	182–183 (EtOH-ether)	$C_{13}H_{11}ClIN_3 \cdot \frac{1}{2}H_2O$ (380.6)	3400,3180–3000,1615,1580, 1470,1425,1305,1290,1200	6.20(s, 2H); 7.1–7.6(m, 3H); 8.1–9.2(m,5H); 12.90(br, 2H)
4d	CH_3	CH_3	72	191–192 (EtOH)	$C_{15}H_{16}IN_3 \cdot H_2O$ (383.2)	3300,1610,1460,1435,1300 1160	2.72(s, 6H); 6.12(s, 2H); 7.30(s, 2H); 8.1–8.7(m, 5H); 12.70(br, 1H)
4e	H	OCH_3	57	143–145[c]	$C_{14}H_{14}IN_3O$ (367.2)	3400,3300,1630,1490,1460, 1440,1270,1205,1160	3.76(s, 3H); 6.11(s, 2H); 6.8–7.5(m, 3H); 7.9–9.1(m, 5H); 12.70(br, 1H)
5a	$C_6H_5CH_2$	---	41	197–198 (EtOH)	$C_{20}H_{18}IN_3$ (427.3)	1635,1500,1490,1470,1445, 1330,1295,1240,1195	5.62(s, 2H); 6.25(s, 2H); 7.1–7.7(m, 9H); 8.0–9.2(m, 5H)
5b	CH_3	---	38	193–195 (EtOH)	$C_{14}H_{14}IN_3 \cdot \frac{1}{2}H_2O$ (360.2)	3500–3260,1635,1485,1440, 1330,1290,1220	3.91(s, 3H); 6.40(s, 2H); 7.1–7.9(m, 4H); 8.1–9.3(m, 5H)
7a	C_6H_5	---	68	186–187 (EtOH)	$C_{20}H_{16}IN_3O \cdot \frac{1}{2}H_2O$ (447.2)	3030,1710,1635,1490,1455, 1305,1220	6.41(s, 2H); 7.1–7.9(m, 9H); 8.1–8.9(m,5H)
7b	4-Cl-C_6H_4	---	64	202–203 (EtOH-H_2O)	$C_{20}H_{15}ClIN_3O$ (475.8)	3025,1700,1640,1600,1500, 1460,1405,1360,1310,1230	6.38(s, 2H); 6.6–7.8(m, 8H), 8.1–9.2(m,5H)
10a	H	H	60	253–254 (EtOH)	$C_{13}H_{19}Br_2N_3$ (3771.1)	3500–2500,1630,1500,1450, 1410,1355,1310,1240,1225	1.72(br, 6H); 4.20(br, 4H); 4.78(s, 2H); 7.3–8.0(m, 4H); 10.20(br, 3H)
10b	H	CH_3	68	252–254 (EtOH)	$C_{14}H_{21}Br_2N_3$ (391.1)	3400–2500,1625,1500,1450, 1410,1355,1310,1240,1225	1.70(br, 6H); 2.45(s, 3H); 3.35(br, 4H); 4.72(s, 2H); 7.1–7.9(m, 3H); 10.25(br, 3H)
10c	H	Cl	67	235–236 (EtOH)	$C_{13}H_{12}Br_2ClN_3$ (411.6)	3450–2500,1635,1515,1450, 1345,1210	1.75(br, 6H); 3.42(br, 4H); 4.73(s, 2H); 7.2–7.9(m, 3H); 10.60(br, 3H)
10d	CH_3	CH_3	68	262–264 (EtOH)	$C_{15}H_{23}Br_2N_3$ (405.2)	3150–2300,1620,1550,1470, 1385,1320,1225,1160	1.75(br, 6H); 2.37(s, 6H); 3.43(br, 4H); 4.78(s, 2H); 7.66(s, 2H); 10.25(br, 3H)

[a] Satisfactory microanalyses obtained: C± 0.41; H± 0.34; N± 0.40; for compound **4e** see text.

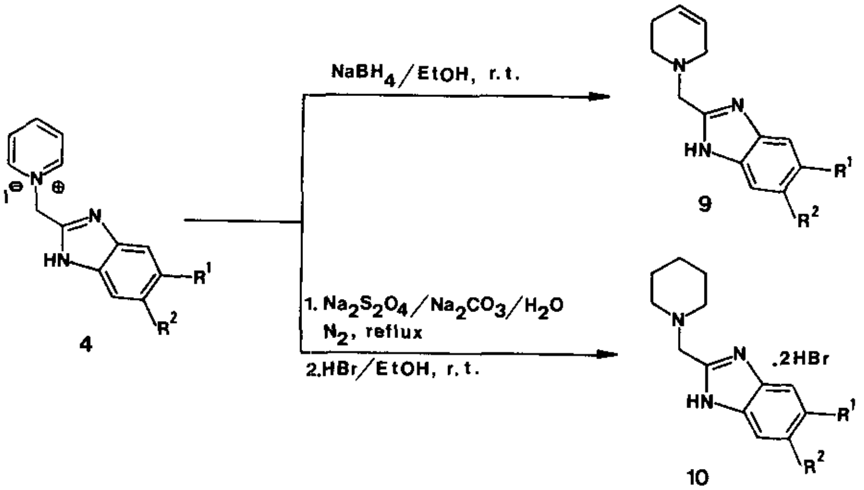
[b] Compounds **4, 5, 7** in DMSO-d_6; compounds **10** in $CDCl_3$.

[c] Decomposition was observed when recrystallization was tried.

MICROANALYSES **Calc. (%)**
Found (%)

COMPOUND	C	H	N
4a	46.31	3.58	12.46
	46.72	3.72	12.06
4b	47.47	4.26	12.02
	47.88	4.01	11.96
4c	41.02	3.17	11.04
	40.78	3.31	10.68
4d	47.01	4.73	10.96
	47.07	4.39	10.84
4e	45.79	3.84	11.44
	46.78	4.68	11.80
5a	56.22	4.24	9.83
	56.29	4.26	9.64
5b	46.68	4.21	11.66
	46.94	4.49	11.56
7a	53.35	3.80	9.33
	53.60	4.01	9.26
7b	50.49	3.17	8.83
	50.40	3.30	8.81
10a	41.40	5.07	11.14
	41.40	5.25	11.09
10b	42.99	5.41	10.74
	42.77	5.30	10.65
10c	37.93	4.40	10.21
	37.90	4.49	10.60
10d	44.46	5.72	10.37
	44.32	5.88	10.73

Acylation[19] of **4a** with benzoyl chloride and 4-chlorobenzoyl chloride was easily undertaken in toluene or acetonitrile in the presence of pyridine. However, under these conditions no reaction was observed with benzenesulphonyl chloride and the starting material was recovered as chloride salt, by halogen interchange.



Reduction of **4a** with sodium borohydride[20] gave the tetrahydropyridine derivative **9** as the major product whereas when the reduction was carried out with sodium dithionite[21] the desired 2-(1'-piperidinylmethyl)benzimidazole derivatives **10** were obtained in good yield.

EXPERIMENTAL

Melting points were determined on a Buchi SMP-20 and are uncorrected. I.R. spectra were recorded on a Perkin-Elmer 700 or 1310 spectrophotometers. ^{1}H-N.M.R. spectra were obtained on Bruker WP60Wc and Farian FT-80 instruments using TMS as internal reference.

Preparation of benzimidazoles 4; General procedure: A mixture of 1-[(methylthio)thiocarbonylmethyl]pyridinium iodide **1** (10 mmol) and the corresponding o-phenylenediamine **2** (10 mmol) was heated under reflux in methanol (30 ml) for 7 h. The reaction mixture was then allowed to cool to room temperature and the precipitate thus obtained was filtered off and recrystallised from the adequate solvent (see table).

1-[(2'-Amino-5'-nitrophenylamino)thiocarbonylmethyl] pyridinium iodide 3f: A mixture of **1** (10 mmol) and 1,2-diamino-4-nitrobenzene (10 mmol) was heated under reflux in methanol (30 ml) for 20 h. After cooling the reaction mixture to room temperature, the precipitate formed was filtered off and recrystallised from ethanol-water (1.45 g, 38 %), m.p. 210-212 °C.

$C_{13}H_{13}IN_4O_8S.½H_2O$	Calc.	C:36.71	H:3.31	N:13.17
(425.2)	Found	C:36.52	H:3.41	N:13.19

I.R. (KBr): ν =3400, 3300, 3180, 1620, 1570, 1500, 1470, 1200 cm^{-1}

^{1}H-N.M.R. (DMSO-d_6): δ = 5.82 (s, 2H); 6.71-6.84 (m, 3H); 7.93 (br, 2H); 7.94-9.03 (m, 5H); 11.73 (br, 1H) ppm.

Alkylation of 1-(2'-benzimidazolylmethyl)pyridinium iodide 4a; General procedure: A suspension of potassium carbonate (2.24 g) and the benzimidazole derivative **4a** (1 g, 3 mmol) in dry acetone (15 ml) was vigorously stirred at room temperature for 1 h. Then, either methyl iodide or benzyl chloride (3 mmol) were added and stirring was continued for further 1 h at room temperature and the inorganic salt was filtered off and washed twice with hot ethanol (50 ml). The filtrate was concentrated and the residue was triturated with ethanol. Recrystallization from ethanol gave the N-alkylated derivatives **5a-b**.

Acylation of 1-(2'-benzimidazolylmethyl)pyridinium iodide 4a; General procedure: A solution of **4a** (1g, 3 mmol) and pyridine (3 ml) in acetonitrile (30 ml) was heated to 70 °C. The corresponding acyl chloride (3.2 mmol) was added and the reaction mixture was heated to 60-70 °C for 30 minutes. After cooling, the precipitate was filtered off. The filtrate was concentrated and the residue was washed with ethanol-water. The remaining solid was recrystallised together with the previously isolated, to give N-acylated derivatives **7a-b**.

1-[Benzyl-2'-(1'-benzylbenzimidazolyl)methyl] pyridinium iodide 6: To a mixture of **5a** (1.38 g, 3.2 mmol) and potassium carbonate (2.24 g) in acetonitrile (20 ml), benzyl chloride (0.45 g, 3.6 mmol) was added and the mixture was stirred at room temperature for 20 h. After that time, the inorganic salt was filtered off and washed with acetonitrile. The acetonitrile phase was concentrated and the oily residue was triturated with methanol. The solid thus formed was recrystallised from ethanol to give **6** (0.63 g, 38 %), m.p. 203-204 °C.

$C_{27}H_{24}IN_3$	Calc.	C:62.67	H:4.67	N:8.12
(517.4)	Found	C:62.32	H:4.78	N:7.84

I.R. (KBr): ν=3040, 1630, 1500, 1490, 1455, 1420, 1325, 1250, 1145, 1030 cm^{-1}

^{1}H-N.M.R. (DMSO-d_6): δ =4.02 (d, 2H); 5.85 (s, 2H); 6.5-7.7 (m, 15H); 7.8-9.2 (m, 5H) ppm.

1-[(Methylthio)thiocarbonyl-2'-benzimidazolylmethyl] pyridinium ylide 8: To a suspension of **4a** (0.67 g, 2 mmol) in 50 % aqueous potassium carbonate solution (20 ml), carbon disulphide (20 ml) and methyl iodide (4 mmol) were added and the reaction mixture was stirred at room temperature for 20 h. The precipitate obtained was filtered and washed with water until neutral. Recristallization from ethanol gave **8** (0.30 g, 44 %), m.p. 218-219 °C.

$C_{15}H_{13}N_3S_2$	Calc.	C:60.16	H:4.37	N:14.03
(299.4)	Found	C:59.90	H:4.79	N:13.99

I.R. (KBr): ν=3160, 1625, 1520, 1470, 1455, 1425, 1280, 1235 cm^{-1}

^{1}H-N.M.R. (DMSO-d_6): δ =2.41 (s, 2H); 6.9-7.6 (m, 4H); 8.9-9.1 (m, 5H); 13.43 (br, 1H) ppm.

2-(1',2',3',6'-Tetrahydropyridyl-1'-methyl)benzimidazole 9: To a solution of the benzimidazole **4a** (3.37 g, 10 mmol) in ethanol (100 ml) was added sodium borohydride (1.51 g, 40 mmol) and the mixture was stirred at room temperature for 30 minutes. The pink solution was then acidulated with acetic acid, the inorganic salt was filtered off, and the filtrate was concentrated. The oily residue thus obtained was solidified by treatment with water and the solid formed was filtered and recrystallised from ethanol-water to give 1.60 g (75 %) of **9**, m.p. 157-158 °C.

$C_{13}H_{15}N_3$	Calc.	C:73.20	H:7.08	N:19.70
(213.3)	Found	C:72.91	H:7.13	N:19.41

I.R. (KBr). ν=3040, 2900, 2820, 1620, 1595, 1540, 1425, 1330, 1270, 1140, 1040, 1005 cm^{-1}

^{1}H-N.M.R. (DMSO-d_6): δ =2.10 (br, 2H); 2.56 (t, 2H); 2.96 (s, 2H); 3.75 (s, 2H); 5.65 (s, 2H); 7.0-7.5 (m, 4H); 12.25 (br, 1H) ppm.

Preparation of 2-(piperidinylmethyl)benzimidazoles 10; General procedure: A mixture of sodium dithionite (24 mmol), sodium carbonate (43 mmol) and the corresponding benzimidazole derivative (2 mmol) in water (125 ml) was refluxed under nitrogen for 15 h. The solution was then concentrated to 90 ml and extracted with methylene chloride (4x50 ml), dried with magnesium sulphate and evaporated to give a residue which was dissolved in ethanol and treated with a slight excess of bromic acid. The dibromohydrate thus obtained was recrystallised from ethanol.

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