Synthesis and Spectral Studies of 2-Mercaptobenzimidazole Derivatives. I.

D. B. Saxena, R. K. Khajuria and O. P. Suri

Regional Research Laboratory, CSIR, Jammu Tawi-180001, India

Received May 22, 1981

The syntheses of some 2-mercaptobenzimidazole (I) derivatives have been described. While preparing such compounds it has been observed that I reacts predominantly as the thione under anhydrous reaction conditions, and as the thiol in the presence of an alkali. Strutures of all of the nine compounds have been established with the help of spectral methods including ^{13}C nmr spectroscopy of the two compounds (II and III).

J. Heterocyclic Chem., **19**, 681 (1982).

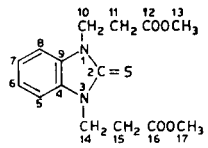
2-Mercaptobenzimidazole derivatives having substituents at nitrogen or sulphur of a thioamide ring are reported (1-5) to exhibit a broad spectrum of biological activity but to our knowledge no derivative of the said compound has been subjected to insecticidal activity screening to date. Keeping this in mind, a few compounds starting from 2-mercaptobenzimidazole (I) have been synthesised and subjected to insecticidal tests.

The derivatives have been prepared under two sets of conditions, one set resulted in substitution mainly at *N*-atoms and the other set yielded *S*-substituted compounds. Substitution at nitrogen is promoted under anhydrous conditions, while the presence of alkali made the reagent attack at the sulphur atom undoubtedly due to the mercaptide anion generated.

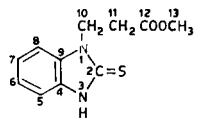
Under the first set of conditions I was allowed to react with (a) methyl acrylate in dimethyl formamide (DMF), (b) acetic anhydride in pyridine, and (c) 1,2-dibromoethane in DMF under anhydrous conditions. Reaction with methyl acrylate gave two compounds (II and III) and those with other reagents IV and V, respectively. The ^1H nmr spectra of compounds II, III and V which displayed a triplet in the region δ 4.07 to 4.62 (J = 6.0 Hz) for two protons of a methylene group and the ir (potassium bromide) spectra which exhibited absorption bands in the region 1325-1320 (-NH-C=S), 1200-1160 (>N-C(S)-NH) and 605-580 (C=S) cm^{-1} in all the compounds indicated the place of substitution at nitrogen rather than sulphur. The unassuming low field absorption signals displayed by the methylene protons attached to nitrogen may be attributed to the free-rotation of N-C bond of $-N-CH_2-CH_2-$ group, thereby bringing the methylene protons under the purview of the deshielding zone of a phenyl ring; this effect is supplemented by anisotropy of the thiocarbonyl group. Substitution at nitrogen was confirmed by ^{13}C nmr spectra of compound II and III (Table 1), which showed the presence of a quaternary carbon in the form of a C=S group in the molecule. The above data unambiguously confirmed that I in the above reaction conditions reacted predominantly as the thione, one of the two possible tautomeric forms.

Table 1

^{13}C NMR Chemical Shifts and Assignments for Compounds II and III



II



III

C-Atom No.	δ (Multiplicity)	C-Atom No.	δ (Multiplicity)
2	169.020 (s)	2	167.790 (s)
4,9	131.746 (s)	4,9	132.507 (s) and 130.628 (s)
5,8	109.318 (d)	5,8	110.225 (d) and 109.483 (d)
6,7	123.024 (d)	6,7	123.409 (d) and 122.879 (d)
10,14	40.362 (t)	10	39.892 (t)
11,15	32.114 (t)	11	32.290 (t)
12,16	171.603 (s) and 171.519 (s)	12	171.547 (s)
13,17	51.928 (q) and 51.723 (q)	13	52.017 (q)

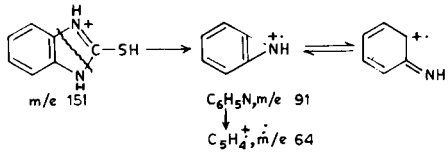
Another set of conditions, condensation of I was carried out with halogenated compounds, namely *n*-butyl bromide, *n*-hexyl bromide, 1,2-dibromoethane and 3-bromopropionic acid in the presence of alkali by the procedure adopted earlier by Knobloch and coworkers (6). Reaction with *n*-butyl bromide gave *S*-butylated compound (VIa, 40.8%) and *N,S*-dibutylated compound (VIb, 4.4%); with *n*-hexyl bromide it gave *S*-hexylated compound (VII); with 1,2-dibromoethane a dimer (VIII) and with 3-bromopropionic acid, *S*-carbomethoxyethyl ether (IX). Compound VIa [mp 134°, lit (6) mp 134°], IX [mp 179°, lit (6) mp 182°], Vb, VII and VIII were identified *via* their ir and ^1H nmr spectra. All these compounds (VIa-IX) showed absorption bands in the region 1270-1250 cm^{-1} in ir spectra indicating the presence of $-SCH_2-$ group duly supported by ^1H nmr which showed a triplet in the region

δ 3.25-3.57 for two protons of the methylene group attached to sulphur (-S-CH_2-CH_2-). In addition to this the ^{1}H nmr spectra of compounds VIa and VII exhibited the presence of a proton on one of the nitrogen atoms of the thioamide ring, which exchanged with deuterium oxide and also the long range coupling of aromatic proton expected with tertiary nitrogen. The above data confirmed that I reacted as the thiol and not as the thione.

I : R_1=R_2=H
II : R_1=R_2=-$CH_2CH_2COOCH_3$
III : R_1=-$CH_2CH_2COOCH_3$; R_2=-H
OR R_1=-H; R_2=-$CH_2CH_2COOCH_3$
IV : R_1=-$COCH_3$; R_2=H
OR R_1=-H; R_2=-$COCH_3$
V : R_1=-CH_2CH_2Br; R_2=-H
OR R_1=-H R_2=-CH_2CH_2Br

VIa : R_1=-H; R_2=-$CH_2(CH_2)_2CH_3$
VIb : R_1=R_2=-$CH_2(CH_2)_2CH_3$
VII : R_1=H; R_2=-$CH_2(CH_2)_4CH_3$
VIII : R_1=-H; R_2= dimer
IX : R_1=-H; R_2=-CH_2CH_2COOH

From the mass spectra of all the compounds it can be concluded that the ion, m/e 151 (2-mercaptobenzimidazolyl) is the most stable fragment. Thus, all the compounds cleave to give the ion, m/e 151 followed by the possible fragments given below.



Insecticidal Activity.

All the compounds, mentioned above, were screened against cotton leaf worm, *Spodoptera litura* for their biological efficacy and were found to be ineffective up to 0.1% concentration.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on Perkin Elmer-377 Grating IR spectrophotometer in potassium bromide. The ^{1}H nmr spectra were measured on T-60A Varian spectrophotometer using tetramethylsilane as the internal reference. The values are reported in δ units. Mass spectra were taken on JEOL JMS-D300 mass spectrometer. The ^{13}C nmr spectra were run on JEOL FX 100 FT nmr spectrophotometer in deuteriochloroform.

2-Mercaptobenzimidazole (I).

This compound was prepared by treating *o*-phenylenediamine with carbon disulphide in the presence of potassium hydroxide by the method of Van Allan and Deacon (7), yield 90%, mp 301-302°, [lit (7) mp 303-304°]; ir: ν max 3070, 1565, 1495, 1440, 1345, 1325, 1250, 1205, 1150, 1100, 950, 910, 810, 735, 695, 645 and 590 cm^{-1}; ^{1}H nmr (DMSO-d_6): 2.68 (broad, 1H, -S*H*), 7.20 (s, 4H, ArH), 9.40 (broad, 1H, collapsed on exchanging with deuterium oxide, -N*H*-); ms: m/e (%) 149 (M-1, 100), 123 (20.41), 122 (29.90), 118 (24.52), 106 (41.12), 96 (11.90), 92 (13.75), 91 (11.84), 90 (8.40), 78 (7.37), 65 (26.76), 64 (12.05), 63 (19.22), 61 (21.20), 52 (8.78).

Anal. Calcd. for $C_7H_6N_2S$: C, 55.97; H, 4.03; N, 18.65; S, 21.35. Found: C, 56.24; H, 4.02; N, 18.58; S, 21.39.

2-Mercapto-1,3-(*N,N*^{1}-dicarbomethoxyethyl)benzimidazole (II).

A mixture of I (1.50 g, 0.01 mole), methyl acrylate (10.0 g, 0.11 mole) and sodium carbonate (2.0 g) in dimethylformamide (200 ml) was heated with stirring at 100° for 6 hours. After removal of DMF under reduced pressure, 200 ml of water was added to the residue and the mixture was acidified with dilute hydrochloric acid to give a colourless powder, which on crystallization from alcohol gave colourless fine needles (2.06 g, 64%), mp 79-80°; ir: ν max 1725, 1470, 1430, 1390, 1325, 1276, 1235, 1190, 1160, 1140, 990, 950, 910, 845, 810, 735, 640, 585 and 540 cm^{-1}; ^{1}H nmr (deuteriochloroform): 2.90 (t, 4H, J = 6.5 Hz, 2-CH_2-CH_2COOCH_3), 3.67 (s, 6H, 2-COOCH_3), 4.60 (t, 4H, J = 6.5 Hz, 2-N-CH_2-CH_2-), 7.30 (s, 4H, ArH); ms: m/e (%) 321 (M-1, 9.19), 307 (22.60), 292 (17.79), 291 (100), 263 (73.73), 237 (35.55), 236 (89.38), 231 (43.46), 205 (22.06), 203 (28.40), 178 (32.65), 176 (23.03), 175 (37.80), 163 (26.02), 161 (23.54), 152 (13.71), 151 (39.44), 134 (16.75), 131 (16.20), 119 (32.23), 118 (21.04), 92 (6.66), 90 (13.08), 87 (39.73), 65 (3.49), 63 (4.99), 59 (26.02), and 55 (39.93).

Anal. Calcd. for $C_{15}H_{18}N_2O_4S$: C, 55.88; H, 5.63; N, 8.69; S, 9.94. Found: C, 56.00; H, 5.64; N, 8.70; S, 9.98.

2-Mercapto-1-(*N*-carbomethoxyethyl)benzimidazole (III).

After the separation of II, the solvent was removed from the mother liquor of the above reaction mixture and the residue crystallized from petroleum ether to give microcrystalline needles (270 mg, 11.4%), mp 115°; ir: ν max 3150, 1720, 1495, 1475, 1460, 1435, 1420, 1370, 1320, 1290, 1222, 1200, 1165, 1130, 1050, 1008, 975, 890, 830, 780, 765, 740, 690, 605, 585 and 530 cm^{-1}; ^{1}H nmr (deuteriochloroform): 2.93 (t, 2H, J = 6.5 Hz, -CH_2CH_2COOCH_3), 3.70 (s, 3H, -CH_2COOCH_3), 4.62 (t, 2H, J = 6.5 Hz, -N-C$H_2$$CH_2$-), 7.30 (s, 4H, ArH), 11.23 (s, 1H, -N*H*-, collapsed on exchanging with deuterium oxide).

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86; S, 13.57. Found: C, 55.76; H, 5.10; N, 11.82, S, 13.62.

2-Mercaptobenzimidazolyl-1-acetate (IV).

Acetate was obtained by the usual method of keeping a solution of I in acetic anhydride-pyridine (1:4) under anhydrous condition at room temperature overnight. The solid thus obtained showed the following characteristics: mp 198-200°; ir: ν 3080, 1720, 1570, 1460, 1405, 1365, 1310, 1300, 1280, 1242, 1205, 1180, 1150, 1105, 1030, 1005, 986, 900, 745, 630, 590 and 580 cm^{-1}; ^{1}H nmr (pyridine-d_5): 3.20 (s, 3H, >N-COCH_3), 5.67 (broad, 1H, >N*H*, collapsed on exchanging with deuterium oxide), 7.25 (s, 4H, ArH).

Anal. Calcd. for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57; S, 16.68. Found: C, 56.42; H, 4.17; N, 14.44; S, 16.69.

2-Mercapto-1-(2-bromoethyl)benzimidazole (V).

A solution of I (1.5 g, 0.01 mole) and 1.2-dibromoethane (2.0 g, 0.01 mole) in DMF (50 ml) was added dropwise to a stirred suspension of sodium hydride (0.24 g, 0.01 mole) in DMF (50 ml) followed by filtration. The residue thus obtained was chromatographed over silica gel (150 g). The fractions, eluted with chloroform containing 1% methanol on evaporation of solvent gave colourless residue, which on crystallization from ethanol gave colourless needles (0.84 g, 32.6%), mp 205°; ir: ν max 3360, 1620, 1600, 1525, 1470, 1455, 1370, 1305, 1250, 1230, 1125, 1090, 750, 650, 620, 585 and 560 cm^{-1}; ^{1}H nmr (trifluoroacetic acid): 4.03 (m, 2H, -CH_2-CH_2Br), 4.35 (m, 2H, -N-C$H_2$$CH_2$Br), 7.26 (s, 4H, ArH); ms: m/e (%) 178 (25.66), 177 (100, M-80), 175 (70.05), 161 (23.66), 150 (6.16), 149 (6.83), 148 (26.62), 143 (14.99), 134 (29.99), 132 (11.97), 131 (36.40), 130 (37.76), 118 (17.24), 117 (25.89), 104 (13.08), 103 (48.53), 102 (15.96), 91 (7.65), 90 (42.20), 82 (31.41), 81 (18.01), 80 (34.00), 77 (15.15), 76 (17.87), 64 (12.84), 63 (20.77), 50 (10.95).

Anal. Calcd. for $C_9H_9BrN_2S$: C, 42.36; H, 3.55; N, 10.98; S, 12.56; Br, 31.22. Found: C, 42.54; H, 3.53; N, 11.02; S, 12.52.

2-*S*-*n*-Butylbenzimidazole (VIa).

It was prepared by refluxing I (0.5 g, 0.0033 mole) and *n*-butyl bromide (0.55 g, 0.004 mole) in 1*N* alcoholic sodium hydroxide (3.3 ml) for 30 minutes by the procedure adopted by Knobloch and co-workers (6). The reaction mixture on work up and crystallization from petroleum ether

gave sandy crystals (0.28 g, 40.8%), mp 134° [lit mp (6) 135°]; ir: ν max 3450, 1605, 1580, 1490, 1420, 1390, 1345, 1260, 1220, 1200, 1090, 1010, 1000, 970, 895, 800, 750, 740 and 590 cm^{-1}; ^1H nmr (deuteriochloroform): 0.87 (t, 3H, J = 6.0 Hz, $-CH_2-CH_3$), 1.00-2.00 [m, 4H, $-CH_2-(CH_2)_2-CH_3$], 3.3 (t, 2H, J = 6.0 Hz, $-S-CH_2-CH_2-$), 7.0-7.34, 7.37-7.63 (m, m, 4H, ArH), 8.86 (broad, 1H, collapsed on exchanging with deuterium oxide, -NH-); ms: m/e (%) 207 (M + 1, 26.95), 206 (M^+, 54.0), 177 (29.17), 164 (29.72), 163 (11.65), 160 (12.35), 159 (100), 152 (14.25), 151 (34.41), 150 (over), 149 (24.33), 132 (17.63), 122 (36.29), 119 (15.20), 118 (19.76), 106 (11.15), 92 (11.08), 91 (11.95), 90 (13.58), 65 (14.76), 64 (10.54), 63 (12.82).

Anal. Calcd. for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58; S, 15.54. Found: C, 64.00; H, 6.86; N, 13.60; S, 15.47.

2-*S*-1-*N*-(Dibutyl)benzimidazole (VIb).

After the crystallization of VIa from the above reaction mixture, the mother liquor on concentration showed single spot on TLC (35 mg, 4.4%); ^1H nmr (deuteriochloroform): 0.90 (t, 6H, J = 6.0 Hz, $2-CH_2-CH_3$), 1.13-2.07 [m, 8H, $2-(CH_2)_2-CH_3$], 3.40 (t, 2H, J = 6.0 Hz, $-S-CH_2-CH_2-$), 4.07 (t, 2H, J = 6.0 Hz, $-N-CH_2-CH_2-$), 7.16 (m, 3H, ArH), 7.67 (m, 1H, ArH, -CH=C-N<).

Anal. Calcd. for $C_{15}H_{22}N_2S$: C, 68.65; H, 8.45; N, 10.68; S, 12.22. Found: C, 68.78; H, 8.48; N, 10.70; S, 12.20.

2-*S*-*n*-Hexylbenzimidazole (VII).

Compound VII was also prepared by the above procedure described for the preparation of VIa and VIb in 40% yield as colourless crystalline plates, mp 105°; ir: ν max 3450, 1605, 1580, 1490, 1425, 1390, 1350, 1340, 1260, 1220, 975, 920, 850, 800, 785, 745, 735, 670, 610 and 590 cm^{-1}; ^1H nmr (deuteriochloroform): 0.80 (t, 3H, J = 6.0 Hz, $-CH_2-CH_3$), 1.0-1.93 [m, 8H, $-(CH_2)_4-CH_3$], 3.44 (t, 2H, J = 6.0 Hz, $-S-CH_2-CH_2-$), 7.03-7.34 (m, 2H, ArH), 7.4-7.7 (m, 2H, ArH), 11.3 (broad, 1H, collapsed on exchanging with deuterium oxide, -NH-); ms: m/e (%) 235 (M + 1, 36.08), 234 (M^+, 61.28), 205 (24.67), 192 (10.31), 187 (100), 177 (35.00), 173 (24.69), 164 (41.52), 163 (16.85), 152 (24.96), 151 (86.73), 149 (44.80), 145 (41.09), 131 (25.01), 122 (28.95), 119 (24.90), 118 (28.29), 106 (13.96), 91 (16.58), 90 (17.79), 65 (17.59), 64 (12.29), 63 (14.99), 55 (17.59).

Anal. Calcd. for $C_{13}H_{18}N_2S$: C, 66.62; H, 7.74; N, 11.95; S, 13.68. Found: C, 66.71; H, 7.71; N, 12.00; S, 13.64.

1,2-Bis-(2-mercaptobenzimidazolyl)ethane (VIII).

This compound was prepared by the method used by Bagrii *et al* (8) for the preparation of dimers of imidazole. Compound VIII was obtained in 10% yield, mp 238-239°; ir: ν max 3450, 1500, 1440, 1400, 1360, 1345, 1270, 1228, 1200, 1123, 1010, 985, 760, 745, 737, 695, 670, 660, 615 and 595 cm^{-1}; ^1H nmr (trifluoroacetic acid): 3.5 (s, 4H, $-S-CH_2-CH_2-S-$), 7.25 (s, 8H, ArH); ms: m/e (%) 326 (M^+, 10.67), 179 (13.64), 178 (30.95), 177 (over), 176 (19.45), 175 (36.14), 151 (17.50), 150 (100), 149 (52.69), 123 (6.42), 122 (41.99), 119 (11.25), 118 (13.79), 91 (9.86), 90 (13.45), 65 (7.27), 64 (6.81), 63 (8.97).

Anal. Calcd. for $C_{16}H_{14}N_4S_2$: C, 58.87; H, 4.32; N, 17.16; S, 19.64. Found: C, 58.58; H, 4.52; N, 16.98; S, 19.83.

Benzimidazolyl-2-thiopropionic Acid (IX).

The Knobloch (6) procedure was adopted for the preparation of this compound, yield 70%, mp 179° [lit (6) mp 182°]; ir: ν max 3450, 1410, 1350, 1310, 1250, 960, 828, 780 and 745 cm^{-1}; ^1H nmr (trifluoroacetic acid): 2.80 (t, 2H, J = 6.5 Hz, $-CH_2-C=O$), 3.45 (t, 2H, J = 6.5 Hz, $-S-CH_2-CH_2-$), 7.40 (s, 4H, ArH); ms: m/e (%) 233 (M + 1, 18.21), 232 (M^+, 74.38), 205 (11.84), 204 (49.25), 178 (15.48), 177 (91.70), 176 (13.03), 175 (33.08), 163 (13.14), 152 (23.86), 151 (56.74), 150 (over), 149 (41.37), 123 (26.76), 122 (61.65), 119 (21.98), 118 (52.42), 106 (32.30), 105 (12.56), 96 (17.48), 92 (23.40), 91 (28.35), 90 (32.11), 78 (16.34), 75 (21.10), 72 (67.94), 65 (41.19), 64 (28.53), 63 (37.43), 55 (100).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60; S, 14.42. Found: C, 54.00; H, 4.51; N, 12.57; S, 14.40.

Acknowledgements.

We are grateful to Dr. C. K. Atal, Director for suggesting this problem and providing us with necessary facilities. We wish to thank Dr. K. L. Dhar for fruitful discussion and Mr. B. P. Saxena for carrying out biological tests. Our thanks are also due to Instrumentation Division for recording the spectra.

REFERENCES AND NOTES

(1) H. Hasegawa, N. Tsuda and M. Hasoya, Japanese Patent 7441, 198 (1974); *Chem. Abstr.*, **82**, 156308k (1975).

(2) K. Hideg, O. Hankovzky, E. Palosi, G. Hajos and L. Szporuy, German Patent 2,429,290 (1975); *Chem. Abstr.*, **82**, 156307j (1975).

(3) M. N. Kosyakovskaya, Ch. Sh. Kadyrov, A. V. Gordeeva, V. N. Balikhina and V. V. Filippov, *Dokl. Akad. Nauk Uzb. SSR* **32**, 34 (1975); *Chem. Abstr.*, **84**, 105500a (1976).

(4) G. Rovnyak, V. L. Naryanana, R. D. Haugwitz and C. M. Cimarusti, U. S. Patent 3,927,014 (1975); *Chem. Abstr.*, **84**, 105596m (1976).

(5) S. C. Bell and P. H. L. Wei, *J. Med. Chem.*, **19**, 524 (1976).

(6) W. Knobloch, G. Winkelmann and K. Rintelen, *Arch. Pharm.*, **291**, 113 (1958).

(7) J. A. Van Allan and B. D. Deacon, *Org. Synth.*, Coll. Vol **4**, 569 (1963).

(8) A. K. Bagrii, G. F. Galenko and P. M. Kochergin, *Depov. Akad. Nauk Ukr.* RSR Ser B, **9**, 801 (1975); *Chem. Abstr.*, **84**, 43959w (1976).