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2-(β -Mercaptoethyl)benzimidazoles

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The four benzimidazoles, 2-(β -mercaptoethyl)-benzimidazole (V), 2-(β -mercaptoethyl)-5-methylbenzimidazole (VI), 5-chloro-2-(β -mercaptoethyl)-benzimidazole (VII) and 5-ethoxy-2-(β -mercaptoethyl)benzimidazole (VIII) were prepared by allowing the appropriate *o*-phenylenediamine to react with β -mercapto propionic acid in hydrochloric acid solution following the method of Phillips (3). The 2-(β -methylthioethyl)benzimidazole (IX) was readily prepared by allowing 2-(β -mercaptoethyl)benzimidazole to react with methyl iodide in alkaline solution.

The *o*-phenylenediamines (I-IV) have been reported previously (4,5,6). It has been found more convenient to prepare the intermediates II and IV by different methods than those reported and these are recorded in the experimental section.

The 2-(β -mercaptoethyl)benzimidazoles were prepared as potential radiation-protection agents and as such were inactive. However, since these compounds may be regarded formally as purine antagonists, they have been screened as antitumor agents. For 2-(β -mercaptoethyl)benzimidazole the following antitumor data were obtained: T/C = 1.06 (SA - 180);

0.29, 0.68, 0.74 (CA - 755); 0.96 (L - 1210). The ED₅₀ was 1.4×10^4 μ g./ml. in the KB cell culture system (slope 0.67) (7).

EXPERIMENTAL (8)

o-Phenylenediamines.

1,2-Diaminobenzene (I).

This compound was practical grade and obtained from Matheson Coleman and Bell.

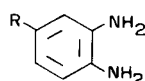
4-Chloro-1,2-diaminobenzene (III).

This compound was prepared by the method of Knoblock (5).

1,2-Diamino-4-methylbenzene (II).

1-Amino-4-methyl-3-nitrobenzene (76 g., 0.5 mole) was dissolved in 40 ml. of 20% sodium hydroxide and 200 ml. of 95% ethanol with warming on the steam bath. A total of 130 g. of zinc dust was added cautiously in small portions. The mixture was refluxed for an additional 45 minutes and filtered hot. After the addition of approximately 3 g. of sodium hydrosulfite, the filtrate was reduced in volume and cooled. The solid was collected and used crude for cyclization.

Cavagnol and Wiselogle (4) reported the preparation of this compound, m.p. 89-89.5°, by a Raney nickel reduction of 1-amino-4-methyl-2-nitrobenzene.

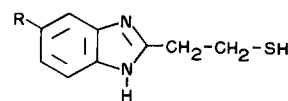
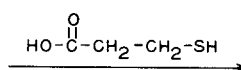


I R = H

II R = CH₃

III R = Cl

IV R = OC₂H₅

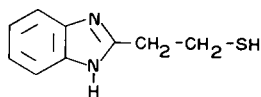


V R = H

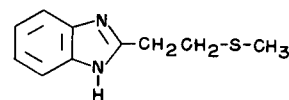
VI R = CH₃

VII R = Cl

VIII R = OC₂H₅



V



IX

1,2-Diamino-4-ethoxybenzene (IV).

To a solution of 1-amino-4-ethoxy-2-nitrobenzene (18.2 g., 0.01 mole) in 55 ml. of concentrated hydrochloric acid was added 25 g. of granulated tin. The temperature was maintained at approximately 60° for 30 minutes with cooling. Then the solution was warmed and the temperature maintained between 70-80° until the tin had dissolved. After an additional 30 minutes' warming, the solution was evaporated almost to dryness. The resulting syrup was poured into 200 ml. of 20% sodium hydroxide solution producing a white solid which was collected and extracted with ether. After removal of the excess ether, the unstable solid was used immediately in the cyclization reaction. Porai-Koshits, *et al.* (6) have prepared this compound, m.p. 79-81°, by an analogous Raney nickel reduction.

General Procedure for the Preparation of 2-(β -Mercaptoethyl)benzimidazoles (3).

A solution containing 0.1 mole of the appropriate *o*-phenylenediamine and 0.15 mole of β -mercapto propionic acid in 100 ml. of 4 N hydrochloric acid was refluxed for 3/4 to 2 hours. After cooling and filtering, the filtrate was made basic with ammonium hydroxide. The solid was collected and recrystallized several times from ethanol or aqueous ethanol. The products are described below.

2-(β -Mercaptoethyl)benzimidazole (V).

The yield of this compound was 30%. It melted at 217-218° and had λ max (95% C₂H₅OH): 208 (ϵ , 23,000); 246 (ϵ , 11,200); 250 (sh) (ϵ , 11,100); 272 (sh) (ϵ , 11,600); 276 (ϵ , 13,600); 282 μ (ϵ , 14,800) and ν (KBr, cm⁻¹) 3400 (m), 3050 (m), 3000 (m), 2900 (m), 2825 (m), 2750 (m), 1625 (m), 1585 (w), 1540 (m), 1475 (w), 1450 (s), 1325 (m), 1270 (s), 1220 (m), 1195 (w), 1145 (w), 1130 (w), 1110 (s), 1030 (m), 1015 (m), 995 (m), 965 (w), 920 (w), 845 (w), 765 (m), 740 (s), 675 (w), 615 (w), 485 (w), 440 (w).

Anal. Calcd. for C₉H₁₀N₂S: C, 60.64; H, 5.65; N, 15.72. Found: C, 61.12; H, 5.30; N, 16.00.

2-(β -Mercaptoethyl)-5-methylbenzimidazole (VI).

This compound melted at 203-204° and had λ max (95% C₂H₅OH): 208 (ϵ , 24,100); 247 (ϵ , 10,100); 253 (sh) (ϵ , 9,500); 278 (sh) (ϵ , 11,700); 281 (ϵ , 12,800); 287 μ (ϵ , 13,000) and ν (KBr, cm⁻¹) 3375 (m), 3025 (m), 2929 (s), 2850 (m), 2775 (m), 1630 (m), 1590 (w), 1540 (m), 1480 (m), 1450 (s), 1425 (s), 1320 (m), 1300 (m), 1275 (m), 1220 (m), 1130 (w), 1025 (w), 1005 (w), 940 (w), 855 (w), 795 (s), 760 (w), 740 (w), 660 (w), 595 (m), 430 (w).

Anal. Calcd. for C₁₀H₁₂N₂S: C, 62.45; H, 6.29; N, 14.57; S, 16.67. Found: C, 62.42; H, 5.52; N, 14.25; S, 16.79.

5-Chloro-2-(β -mercaptoethyl)benzimidazole (VII).

This compound was obtained in 46% yield. It melted at 194-195° and had λ max (95% C₂H₅OH): 209 (ϵ , 24,400); 249 (ϵ , 9,450); 254 (sh) (ϵ , 8,980); 283 (ϵ , 12,800); 290 μ (ϵ , 12,500) and ν (KBr, cm⁻¹) 3400 (m), 3100 (m), 3025 (m), 2925 (m), 2870 (m), 2750 (m), 1625 (w), 1580 (w), 1540 (m), 1475 (m), 1450 (s), 1425 (s), 1320 (m), 1290 (m), 1275 (m), 1220 (m), 1060 (m), 1020 (w), 920 (m), 850 (w), 800 (m), 700 (w), 600 (w).

Anal. Calcd. for C₉H₉ClN₂S: C, 50.82; H, 4.26; N, 13.17. Found: C, 51.18; H, 4.43; N, 13.38.

5-Ethoxy-2-(β -mercaptoethyl)benzimidazole (VIII).

The yield of this compound was 4%. It melted at 189-190° and had λ max (95% C₂H₅OH): 209 (ϵ , 24,200); 247 (ϵ , 11,000); 291 (ϵ , 14,600); 296 μ (sh) (ϵ , 13,400) and ν (KBr, cm⁻¹) 3375 (m), 2975 (s), 2925 (s), 2875 (s), 2750 (m), 1625 (s), 1590 (m), 1530 (m), 1495 (s), 1450 (s), 1400 (m), 1270 (m), 1220 (m), 1170 (s), 1110 (m), 1040 (s), 960 (m), 900 (w), 835 (m), 810 (m), 680 (w), 660 (w), 625 (w), 605 (w), 435 (w).

Anal. Calcd. for C₁₁H₁₄N₂OS: C, 59.43; H, 6.35; N, 12.60; S, 14.42. Found: C, 59.92; H, 6.09; N, 12.16; S, 14.24.

2-(β -Methylthioethyl)benzimidazole (IX).

To a suspension containing 5 g. (0.028 mole) of 2- β -mercaptoethylbenzimidazole in 125 ml. of concentrated ammonium hydroxide was added a solution containing 4.3 g. (0.03 mole) of methyl iodide in 12 ml. of dioxane over a period of 20 minutes. The mixture was maintained at approximately 42° for 1 hour, filtered to remove starting material and the filtrate allowed to stand. The small amount of precipitate, which formed, was recrystallized several times from ethanol-water (norite), m.p. 166-167°. The compound had λ max (95% C₂H₅OH): 208 (ϵ , 23,500); 243 (ϵ , 12,300); 249 (sh) (ϵ , 11,700); 271 (sh) (ϵ , 11,230); 274 (ϵ , 13,500); 280 μ (ϵ , 14,800) and ν (KBr, cm⁻¹) 3400 (w), 3050 (m), 2910 (s), 2825 (s), 2750 (s), 1625 (m), 1580 (m), 1540 (m), 1480 (m), 1425 (s), 1330 (m), 1275 (s), 1225 (s), 1155 (w), 1105 (w), 1030 (m), 1000 (m), 930 (m), 765 (m), 750 (s), 740 (s), 620 (w), 435 (w).

Anal. Calcd. for C₁₀H₁₂N₂S: C, 62.45; H, 6.29; N, 14.57. Found: C, 62.50; H, 6.22; N, 14.29.

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- (2) Communications concerning this paper should be directed to Professor Raymond N. Castle.
- (3) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).
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- (7) The screening data were kindly supplied by Dr. J. E. Leiter, CCNSC, National Institute of Health, Bethesda, Md.
- (8) All melting points are uncorrected. The infrared spectra were determined with a Perkin-Elmer 337 Spectrophotometer. The ultraviolet spectra were taken in the solvent indicated with a Bausch and Lomb Spectronic 505 Spectrophotometer.

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