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The reaction of carbon suboxide with 2-substituted benzimidazoles was investigated. By this reaction 1,3-diazino- (pyrimido-), 1,3-oxazino- and 1,3-thiazinobenzimidazole-1,3-diones are obtained.

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It is well known that benzimidazole derivatives are an important class of heterocyclic compounds which have anticonvulsant [2], sedative [3], immunosuppressive [4], antitumour [5] and antihistaminic [6] activity.

Due to their biological interest and as part of our general studies on the reactivity of carbon suboxide [7] with bifunctionalized compounds, we investigated the reaction of carbon suboxide with 2-substituted benzimidazoles to provide 1,3-diazino- (pyrimido-), 1,3-oxazino- and 1,3-thiazinobenzimidazole-1,3-diones.

By reacting equimolar amounts of 2-amino-, 2-hydroxy- or 2-mercaptobenzimidazoles **1a-c** with carbon suboxide (**2**), in anhydrous acetonitrile solutions and in the presence of a Lewis acid (anhydrous aluminum chloride), heterocyclic compounds **3a-c**, along with small amounts (10-20%) of malonic derivatives **4a-c** were obtained in one step and in satisfactory yields (50-85%).

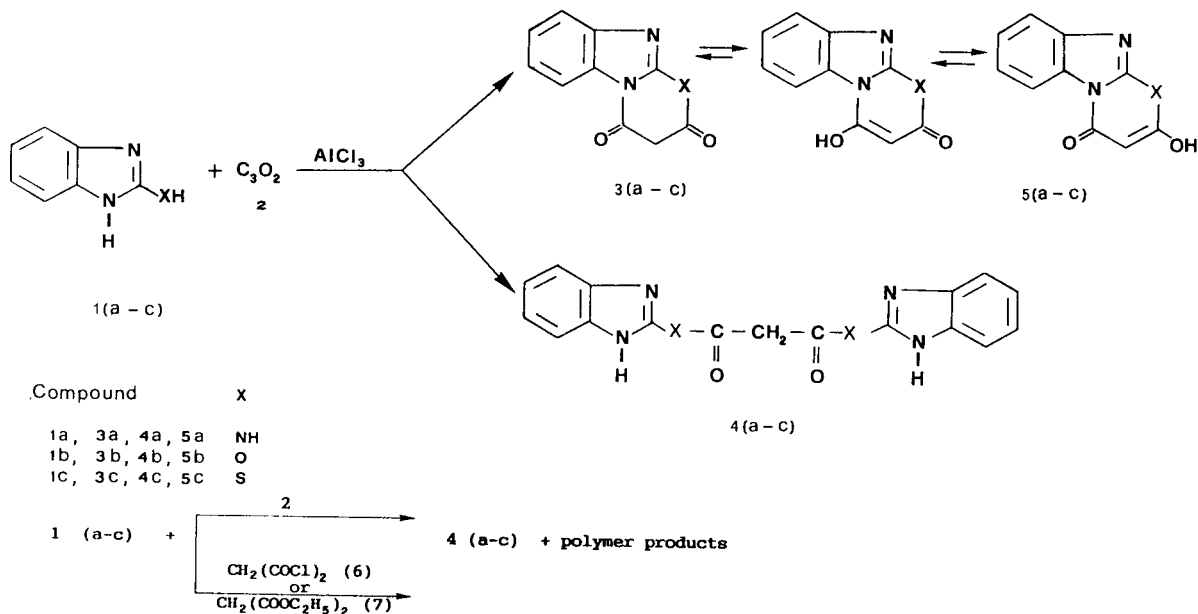
When the reaction was carried out without the Lewis acid, we obtained the starting compounds, along with small quantities of the malonic derivatives **4a-c** and polymer products difficult to separate. The same behaviour

was observed in the reaction between benzimidazole derivatives **1a-c** and malonyl chloride (**6**) or diethyl malonate (**7**).

Compounds **3a-c** were easily separated from the malonic derivatives **4a-c** by flash column chromatography and their structures agreed with <sup>1</sup>H nmr, ir and mass spectra.

The ir and <sup>1</sup>H nmr spectra show that compounds **3a-c** existed as a mixture of the two tautomeric forms **5a-c**. This behaviour has already been observed in our previous work [8]. In fact the ir spectra show the OH band at 3400 cm<sup>-1</sup> in addition to the characteristic band of amidic ester C=O groups between 1700 and 1760 cm<sup>-1</sup>. The <sup>1</sup>H nmr spectra show the characteristic signals of both the methine and the methylene protons at δ 8.42 and 3.42 ppm, respectively, in a 1:1 ratio, between an OH signal at 5.20 ppm. The uv spectra exhibit a bathochromic effect when the ethanol solution of compounds **3a-c** (pH 7) is treated with 0.1N aqueous sodium hydroxide up to pH 12. The maxima values become the initially observed values upon acidification to pH 1.0 with 0.1N hydrochloric acid.

Scheme



## EXPERIMENTAL

Melting points were obtained on a Kofler apparatus and are uncorrected. The  $^1\text{H}$  nmr spectra were recorded on a Varian Unity 300 spectrometer using tetramethylsilane as the internal standard. The ir spectra were run using Nujol mulls on a Perkin-Elmer 1310 spectrophotometer and the representative absorption bands are given. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6D instrument at 70 eV, using a direct-inlet system. The uv spectra were recorded on a Carlo Erba Spectracompt 602. Elemental analyses were carried out on a Carlo Erba model 1106 Elemental Analyzer.

Reagent-grade commercially available reagents and solvents were used. Carbon suboxide (**2**) was prepared from pyrolysis of *O*-acetyltartaric anhydride [9].

1,2,3,4-Tetrahydropyrimido[1,2-*a*]benzimidazole-1,3-dione (**3a**) and *N,N*-Bis-(2-benzimidazolyl)propanediamide (**4a**).

Compound **2** (45 mmoles) was added during two hours to a stirred solution of **1a** (45 mmoles) in anhydrous acetonitrile (400 ml) cooled at 0°, in the presence of a catalytic amount of aluminum chloride. At completion, the mixture was strongly stirred at 0° for two hours and at room temperature for 12 hours. After solvent evaporation the residue was flash chromatographed (ethyl acetate and methanol as eluants) and gave **3a** as yellow crystals in 85% yield, mp 320-321°; ir (nujol):  $\nu$  3400 (OH), 1700-1690 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  12.00 (s, 1H, NH, deuterium oxide exchanged), 8.42 (s, 1H, CH=CO), 7.3 (m, 4H, Ar-H), 5.06 (s, 1H, OH, deuterium oxide exchanged), 3.48 (s, 2H,  $\text{CH}_2\text{-CO}$ ); ms:  $m/z$  201 ( $M^+$ ); uv (ethanol):  $\lambda$  max 235 ( $\epsilon$ , 1,250), 268 ( $\epsilon$ , 5,300) ( $pH$  1.0 and  $pH$  7.0);  $\lambda$  max 258 ( $\epsilon$ , 3,200), 302 ( $\epsilon$ , 6,950) ( $pH$  12.0).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_7\text{N}_3\text{O}_2$ : C, 59.70; H, 3.51; N, 20.89. Found: C, 59.67; H, 3.60; N, 20.90.

The fraction eluated with ethyl acetate gave **4a**, as a yellow substance, in 10% yield, mp 284-286°; ir (nujol):  $\nu$  3280 (NH), 3150 (NH), 1670  $\text{cm}^{-1}$  (CO);  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  12.00 (s, 2H, 2 NH, deuterium oxide exchanged), 10.50 (s, 2H, 2 NH, deuterium oxide exchanged), 7.38 (m, 8H, 2 Ar-H), 3.30 (s, 2H,  $\text{CH}_2\text{-CO}$ ).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{14}\text{N}_6\text{O}_2$ : C, 61.07; H, 4.22; N, 25.14. Found: C, 60.91; H, 4.31; N, 25.02.

1,2-Dihydro-3*H*-[1,3]oxazino[3,2-*a*]benzimidazole-1,3-dione (**3b**) and Bis-2-benzimidazolyl Propanedioate (**4b**).

A solution of **1b** (50 mmoles) in anhydrous acetonitrile (500 ml) was treated with **2** (50 mmoles) and worked up in the same manner as described above. After solvent evaporation the residue was flash chromatographed (ethyl acetate and methanol as eluants) and gave **3b** as brown crystals in 65% yield, mp 315-317°; ir (nujol):  $\nu$  3400 (OH), 1740, 1670  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  8.10 (s, 1H, CH=CO), 6.86 (m, 4H, Ar-H), 5.20 (s, 1H, OH, deuterium oxide exchanged), 3.42 (s, 2H,  $\text{CH}_2\text{-CO}$ ); ms:  $m/z$  202 ( $M^+$ ); uv (ethanol):  $\lambda$  max 281 ( $\epsilon$ , 5,360) ( $pH$  1.0 and  $pH$  7.0);  $\lambda$  max 304 ( $\epsilon$ , 6,900) ( $pH$  12.0).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_6\text{N}_2\text{O}_3$ : C, 59.41; H, 2.99; N, 13.86. Found: C, 59.25; H, 3.01; N, 13.85.

The fraction eluated with ethyl acetate gave **4b** as a light brown substance, in 20% yield, mp 130-131°; ir (nujol):  $\nu$  3150 (NH), 1740  $\text{cm}^{-1}$  (CO);  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  10.52 (s, 2H, 2 NH, deuterium oxide exchanged), 6.80 (m, 8H, 2 Ar-H), 3.33 (s, 2H,  $\text{CH}_2\text{-CO}$ ).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_4$ : C, 60.71; H, 3.60; N, 16.66. Found: C, 60.60; H, 3.80; N, 16.45.

1,2-Dihydro-3*H*-[1,3]thiazino[3,2-*a*]benzimidazole-1,3-dione (**3c**) and Bis-(2-benzimidazolylmercaptocarbonyl)methane (**4c**).

A solution of **1c** (45 mmoles) in anhydrous acetonitrile (400 ml) was treated with **2** (45 mmoles) and worked up in the same manner as described above. After evaporation of the solvent the residue was flash chromatographed (ethyl acetate and methanol as eluants) and gave **3c** as yellow crystals in 52% yield, mp 294-296°; ir (nujol):  $\nu$  3400 (OH), 1760, 1690  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  8.00 (s, 1H, CH=CO), 7.10 (m, 4H, Ar-H), 4.60 (s, 1H, OH, deuterium oxide exchanged), 3.53 (s, 2H,  $\text{CH}_2\text{-CO}$ ); ms:  $m/z$  218 ( $M^+$ ); uv (ethanol):  $\lambda$  max 247 ( $\epsilon$ , 9050), 306 ( $\epsilon$ , 17750) ( $pH$  1 and  $pH$  7);  $\lambda$  max 262 ( $\epsilon$ , 12350), 321 ( $\epsilon$ , 23050) ( $pH$  12).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_6\text{N}_2\text{O}_2\text{S}$ : C, 55.05; H, 2.77; N, 12.84. Found: C, 55.10; H, 2.90; N, 12.73.

The fraction eluated with ethyl acetate gave **4c** as a white substance, in 20% yield, mp 272-275°; ir (nujol):  $\nu$  3150 (NH), 1700  $\text{cm}^{-1}$  (CO);  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  12.48 (s, 2H, 2 NH, deuterium oxide exchanged), 7.08 (m, 8H, 2 Ar-H), 3.34 (s, 2H,  $\text{CH}_2\text{-CO}$ ).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_2\text{S}_2$ : C, 55.44; H, 3.28; N, 15.21. Found: C, 55.35; H, 3.21; N, 15.23.

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