

Reaction of 2-Mercaptobenzimidazole with Ethyl Phenylpropiolate†

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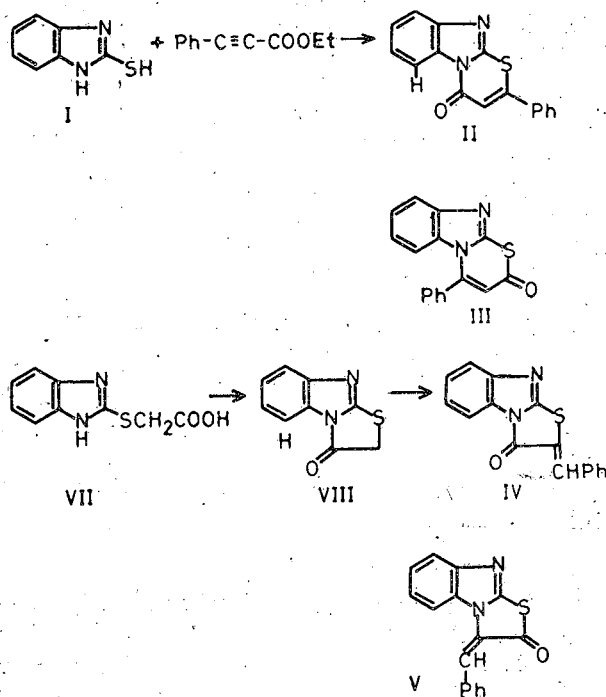
The reaction of 2-mercaptobenzimidazole (I) with phenylpropionic ester results in the formation of 2-phenyl-thiazino[3, 2-*a*]benzimidazol-4-one (II). The structure 4-phenyl-2*H*-1-thiapyrimido[1,2-*a*]benzimidazol-2-one (III) assigned by earlier workers [*J. heterocycl. Chem.*, 15 (1978), 849] is shown to be in error.

IN a recent publication, Al-Jallo and Muniem have reported the reaction of 2-mercaptobenzimidazole with ethyl phenylpropiolate to yield 4-phenyl-2*H*-1-thiapyrimido[1,2-*a*]benzimidazol-2-one (III) in good yield¹. This result was surprising in view of our earlier experience with the addition of dinucleophiles of various kinds to acetylenic esters²⁻⁵. Of the many possibilities in such reactions, the results of Al-Jallo and Muniem pointed to a preferential predilection for the NH group to add to the triple bond followed by cyclization of the ester function on the mercapto group. This then would be one of the rare instances where nitrogen participates in preference to sulphur in the initial conjugate addition to the triple bond.

In our hands, reaction of 2-mercaptobenzimidazole with ethyl phenylpropiolate yielded a product, m.p. 195° different from the reported m.p. (223-24°)¹. The molecular formula and molecular weight (mass spectrum) indicated a product isomeric with the reported compound. We considered all the four possibilities II-V before arriving at the correct structure II for this product.

Unlike in the case of the reported compound, our compound exhibited in its PMR a signal for the C-6 proton on the aromatic ring significantly deshielded to a value of δ 8.9 close to the value of δ 8.84 observed^{3,6} in the case of a similar compound obtained as a by-product in the reaction of diethyl and dimethyl acetylenic esters with 2-mercaptobenzimidazoles. This observation rules out structures (III) and (V) since in these compounds the C-6 proton will not be deshielded; in fact it may be under the shielding influence of the phenyl ring current¹. Of the remaining, it was possible to rule out structure (IV) which we synthesised by known and unambiguous routes⁷⁻⁹ and showed by direct comparison to be different. Compound (IV) also shows an expected deshielded 5-proton; however the deshielding influence of the C=O in the five-membered ring is less than that in the six-membered compound (II).

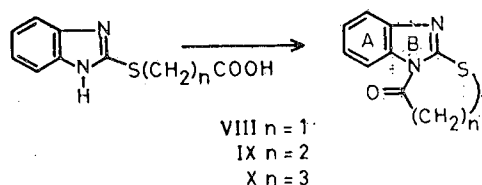
As further evidence for the correct assignment of the six-membered structure (II) for the product,



we resorted to a study of the ¹³C NMR spectrum of this compound. By correlation with the now well-established studies for similar compounds, it is possible to distinguish between the five- and six-membered structures by considering the coupling of the (C₃-H) with the (lactam) carbonyl carbon. The ²J_{CH} is known to be small (\ll 1 Hz) in the cases like II and is often not resolved. On the other hand ³J_{CH} of structure (IV) would be of the order of 6 Hz (refs 3,10). For our product the carbonyl carbon resonance signal shows itself at 159.8 (compared to 159.1 in the ester analogue⁹) and in the gated decoupled spectrum no resolution of this resonance signal is apparent, indicating a coupling of \ll 1 Hz, and the correctness of structure (II).

The deshielding effect of the carbonyl function on the *peri*-proton is a well-documented phenomenon and is possibly the result of various factors¹¹. Never-

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theless, it was of interest to determine the effect of the C-ring size on the anisotropic deshielding by carbonyl group of the *peri*-protons. For this purpose we synthesised in addition to compound (VIII) the two higher homologous compounds (IX) and (X) by cyclization of benzimidazole mercapto-propionic and butyric acids respectively with pyridine and acetic anhydride.

Examination of the PMR spectra of VIII, IX and X in CDCl_3 solution pointed out that the deshielding effect on the *peri*-proton was in the following order IX (six-membered $\delta 8.3$) > X (seven-membered 8.14) > VIII (five-membered 7.94). If the deshielding effect on the proton in the *peri*-position is indeed due only to the steric compression due to the carbonyl group fixed in a rigid position, and to its spatial proximity, one would expect such effect to increase in the order VIII < IX < X. The intermediate value for X could be possibly due to buckling of the seven-membered ring to reduced steric hindrance between the carbonyl group and the C-7 proton in this ring system.

It was also interesting to note that the anisotropic deshielding effect of the carbonyl group on the *peri*-proton was greater for II compared to its dihydro-derivative (IX), part of it at least being due to the increased rigidity imposed by the more aromatic C-ring in II.

Experimental Procedure

PMR spectra were run on a Varian A 60 spectrometer and ^{13}C spectra on a Bruker WH 90 spectrometer at 22.63 MHz using concentrated solutions in CDCl_3 . Chemical shifts are in ppm downfield from TMS as internal standard. ^{13}C shifts were obtained using broad band decoupling while coupling information was gathered using gated decoupling techniques. Mass spectra were taken on a Varian Mat CH-7 spectrometer and IR spectra (ν_{max} in cm^{-1}) on a Perkin-Elmer infracord spectrometer.

2-Phenylthiazino [3,2-*a*] benzimidazol-4-one (II)—A mixture of 4.5g (0.03 mol) of 2-mercaptobenzimidazole and 5.1g (0.03 mol) of ethyl phenylpropiolate was heated at 200° for 12 hr, the solid residue obtained on cooling crystallized from ethanol to yield 5 g of II, m.p. 195° (Found : C, 69.12; H, 3.95; N, 10.22. $\text{C}_{16}\text{H}_{10}\text{N}_2\text{OS}$ requires C, 69.06; H, 3.62; N, 10.07%); M^+ 278; ν_{CO} 1680; PMR (CDCl_3): 6.95 (C-3 H, *s*); 7.16 to 7.8 (8 aromatic H, *m*); 8.9 (C-6 H, *m*); ^{13}C NMR (CDCl_3): C(3) 122 (*d*); C₄(C=O) 159.8 (*s*).

2-Benzylidene-2,3-dihydrothiazolo[3,2-*a*]benzimidazol-3-one (IV)—A mixture of 15g (0.1 mol) of 2-mercaptobenzimidazole and 9.5 g (0.1 mol) of Cl_2CH_2 -

COOH in 80 ml 10% aq. sodium hydroxide was heated for 2 hr on a steam-bath, cooled, acidified with 10 ml conc. HCl and filtered. The residue was washed with chilled water, dried and crystallized from ethanol to yield 15 g of benzimidazolemercapto acetic acid (VII) m.p. $185-87^\circ$ (lit⁷ m.p. 190°).

VII (10g) 15 ml pyridine and 10 ml acetic anhydride were heated together on a water bath for 1 hr and cooled. The solid was filtered off, dried and crystallized to yield 4g of 2,3-dihydrothiazolo [3,2-*a*] benzimidazol-3-one (VIII), m.p. 180° (lit⁸ m.p. 181°) (Found : C, 56.70; H, 3.43; N, 14.46. Calc. for $\text{C}_9\text{H}_6\text{N}_2\text{OS}$: C, 56.84; H, 3.18; N, 14.73%); M^+ 190; ν_{CO} 1740; PMR (CDCl_3): 4.34 (2H, CH_2S), 7.2 - 7.5 (3 aromatic H, *m*) 7.94 (1-H, 5-ArH, *m*).

A mixture of 1.8g of VIII, 1.1g of benzaldehyde and 1g of sodium acetate in 20 ml ethanol was heated under reflux for 6 hr and cooled. The solid was filtered off, washed with water and crystallized from ethanol to yield 1.5 g of 2-benzylidene-2,3-dihydro thiazolo [3,2-*a*] benzimidazol-3-one (IV), m.p. $216-18^\circ$ (lit⁹ m.p. $216-17^\circ$) (Found : C, 69.44; H, 3.91; N, 10.18. Calc. for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{OS}$: C, 69.06; H, 3.8; N, 10.06%).

2,3-Dihydro [4H]-1,3-thiazino-[3,2-*a*] benzimidazol-4-one (IX)—A mixture of 10g of benzimidazole-2-mercapto propionic acid⁹, 15 ml of pyridine and 10 ml of acetic anhydride was heated on a water-bath for 1 hr, cooled, solid filtered and crystallized from ethanol to yield 5g of IX m.p. $164-66^\circ$ (Found : C, 58.86; H, 4.23; N, 13.77. $\text{C}_{10}\text{H}_8\text{N}_2\text{OS}$ requires C, 58.82; H, 3.95; N, 13.72%); M^+ 204; ν_{CO} 1720; PMR (CDCl_3): 3.3 (4H, $\text{CH}_2\text{S} + \text{CH}_2\text{CO}$; *m*), 7.2 - 7.6 (3H, Ar-H, *m*) 8.3 (1H, C₆-H, *m*).

2,3,4,5-Tetrahydro-1,3-thiazepino[3,2-*a*]benzimidazol-5-one (X)—To a solution of 5.6g of potassium hydroxide in 150 ml of ethanol was added with stirring 15 g of 2-mercaptobenzimidazole followed by 19.5 of ethyl bromobutyrate. After heating under reflux overnight, the solvent was evaporated, the residue treated with water and the solid filtered and crystallized from hexane to yield 20g of 2-(ω -carboxybutyl mercapto)-benzimidazole, m.p. 80° (Found : C, 59.20; H, 6.39. $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2\text{S}_2$ requires C, 59.08; H, 6.10%).

To a solution of 1g of sodium in 100 ml of ethanol was added 10g of the above ester and the resulting clear solution heated under reflux overnight, solvent evaporated to dryness, water added to the residue and the solution made acidic to pH 5.0 with 2N aq. HCl. The resulting solid was filtered and crystallized from ethanol to yield 6 g of 2-(ω -carboxybutyl-mercapto)benzimidazole, m.p. $134-37^\circ$ (Found : C, 55.89; H, 5.52; N, 12.24. $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ requires C, 55.93; H, 5.12, N, 11.86%).

A mixture of 6g of the above acid, 6 ml of acetic anhydride and 12 ml of pyridine was heated on a water-bath for 2 hr, cooled and poured into ice water. The gummy solid which separated out on keeping overnight was filtered, washed with a saturated aq. solution of NaHCO_3 and water and recryst-

tallized from benzene-hexane, m.p. 91-93°, yield 1.5g (Found : C, 60.55; H, 4.94; N, 12.77. $C_{11}H_{10}N_2OS$ requires C, 60.54; H, 4.62; N, 12.84%; M^+ 218; ν_{CO} 1700; PMR ($CDCl_3$) : 2.4 (2H — CH_2 , *m*), 3.2 (4H $CH_2S + CH_2CO$, *m*), 7.3 to 7.8 (3H, Ar. H; *m*) 8.14 (1H, C_7 -H, *m*).

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