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ADDITION PRODUCTS OF BENZIMIDAZOLE-2 (2H)-THIONE AND ACETYLENE DICARBOXYLIC ESTERS[1]

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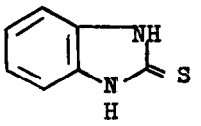
In a recent publication[2], McKillop et al. have reported that the reaction of benzimidazole-2 (2H) thione (1) with dimethyl acetylenedicarboxylate (DMAD) gives rise to a mixture of two products in varying proportions depending upon the solvent, acetic acid or methanol. One of the products, m.p. 192-193°, was obtained pure by fractional crystallization and shown to be 2a, in agreement with an earlier study[3], partly using synthetic evidence but mainly on the basis of X-ray crystallography. The geometry of the exocyclic double bond in 2a unfortunately was not described. The second product of the DMAD reaction was not isolated in the pure state, but the presence of a very low field aromatic (H_A) resonance at δ 8.84 in the ^{1}H NMR spectrum of the mixture of products prompted these authors to consider structure 4a for this component. However they pointed out that structure 5a could not be excluded as anisotropic shielding of H_A would be anticipated in this structure as well. Additionally it may be noted that although structure 3a was mentioned, it was not considered in the discussion. 3a cannot be eliminated as a possibility especially if it has the geometry shown.

We have been interested in the use of ^{13}C NMR spectroscopy for the elucidation of structures of addition products of a variety of thiocarbamoyl and other dinucleophiles to acetylenedicarboxylic esters and have shown recently[4] that thioureas in general give rise to carboxymethylidenethiazolinones 6, incorporating a fumarate unit (Z configuration). The chemical shift of the lactam C=O carbon and more particularly its coupling with a neighbouring proton were used to assign structures 6 uniquely, ruling out several alternative possibilities, among them mainly 7 which was a strong contender[5]. As part of this exercise, we have studied the addition of 1 to DMAD and the diethyl ester (DEAD) and wish to communicate our results briefly.



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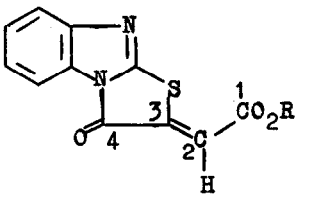
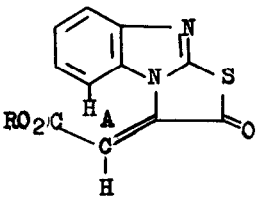
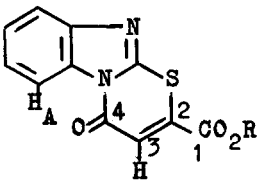


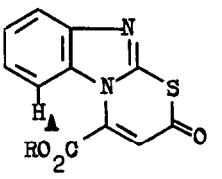
2 a,b



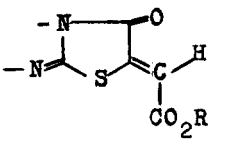
3 a,b



4 a,b



5 a,b



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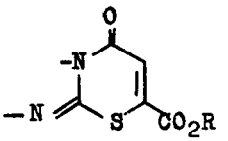
(Series a : R = Me; b : R = Et)



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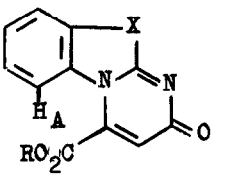

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Reaction of equimolecular amounts of 1 with DMAD in methanol or acetic acid gave mixtures of 2a and 4a in approximately the same ratios as reported[1] (^{1}H NMR analysis). Crystallization of the crude product that came out of the reaction in acetic acid, from acetone gave 2a[6], m.p. 191-193°; ν_{CO} 1740, 1690 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 270, 334 (log ε 4.22, 3.48), λ_{min} 299 (log ε 3.28); mass spectrum m/e at 260 (M$^+$; 100%), 229 (20%), 201 (40%), 174 (85%), 126 (40%). The acetic acid mother liquors were combined and concentrated to give a crop from which more 2a was crystallized out with acetone. The more soluble product was then recovered and recrystallised thrice from the same solvent to give pure 4a, m.p. 171-173°; ν_{CO} 1745, 1710 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 255, 268 (inflex), 298-315, 360 (inflex) (log ε 4.42, 4.32, 3.52, 3.25); mass spectrum m/e 260 (M$^+$, 100%), 201 (25%), 173 (48%), 172 (26%), 129 (40%). The reaction of 1 with DEAD in acetic acid or ethanol likewise gave a mixture of 2b and 4b. The product from the acetic acid reaction was separated as before into 2b (from acetone), m.p. 169-171° and 4b (from acetone;

85% pure), m.p. 128-134°. Relevant NMR spectral data of the four products are collected in the Table[7].

Table: NMR spectral data of thiazolobenzimidazoles 2a, 2b and thiazinobenzimidazoles, 4a and 4b.

Compd. No.	^{13}C				^{1}H		
	δC(1)	δC(2)	δC(3)	δC(4)	δH_A	δH(C-2)	δH(C-3)
2a	165.8 (q, J = 4 Hz)	121.5 (d, J = 174 Hz)	-	157.4 d, $J_{C(4)H(C-2)}$ = 6 Hz	-	7.15 (s)	-
2b	165.2 (t, J = 3 Hz)	122.1 (d, J = 174 Hz)	-	157.8 d, $J_{C(4)H(C-2)}$ = 6 Hz	7.92[11] (m)	7.00 (s)	-
4a	161.8 (m)	-	121.5 (d, J = 177 Hz)	159.1 (s)	8.45 (m)	-	7.40 (s)
4b	161.2 (m)	-	121.1 (d, J = 176 Hz)	158.4 (s)	8.30 (m)	-	7.25 (s)

The ^{13}C NMR spectrum of 2a showed two low field signals, a quartet due to C-1[8] and a doublet for C-4 with $J_{C(4)H(C-2)}$ = 6 Hz. C-1 and C-4 in 2b were correspondingly seen respectively as a triplet and a doublet with $J_{C(4)H(C-2)}$ = 6 Hz. The observed coupling of the lactam C atom clearly supports the thiazolinone structures 2a and 2b with a fumarate geometry (Z isomer) and rules out the E isomer (expected J ~12 Hz) and thiazinone possibilities 4 and 5 (expected 2 bond $J_{CH} \leq$ 1 Hz)[4].

The ^{13}C NMR spectrum of 4a showed a multiplet and a singlet in the C=O region. The former is clearly due to C-1, coupled to H(C-3) and CH_3. Thus the singlet is to be ascribed to the other carbonyl carbon atom. The spectrum of 4b had similar features in the CO region. Structures 4a and 4b are thus supported, since $^{2}J_{CH}$ is known to be small in such systems and is often not resolved. Structures 3a and 3b are ruled out automatically, since these should show $^{3}J_{CH}$ of the order of 6 Hz. The remaining possibilities 5a and 5b are unlikely since it is well-known that sulphur is more nucleophilic than nitrogen in cyclic and acyclic thioureas. More importantly, in several published examples of 8 (X = S)[4,9] and (X = NH)[10], there is no signal in the ^{1}H NMR spectrum below δ 7.7. On the other hand, 4a and 4b as well as analogous pyrimidobenzimidazoles[10] do exhibit a proton multiplet

around 8.5 ppm. We have thus succeeded in isolating the second component from the reaction of 1 with DMAD and using NMR spectroscopy to establish its structure as 4a.

We have also observed that 2a and 4a were unchanged after refluxing in o-dichlorobenzene solution for 1 hour. Treatment of 2a with catalytic amount of sulphuric acid in refluxing methanol for 8 hr. led to a mixture of 2a (47%) and 4a (53%). Similar treatment of 4a for 16 hr gave a mixture of 2a (38%) and 4a (62%), demonstrating that 4a was somewhat stabler than 2a. The changes presumably occur by attack of the lactam C=O group by methanol followed by recyclization involving the original carbomethoxy group. An alternative possibility of acid-catalyzed cleavage of S-C(3)/C(2) bond followed by readdition of sulphur to the other centre cannot be ruled out.

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6. All new compounds had correct elemental analyses.
7. ^{1}H NMR spectra were run on a Varian A60 spectrometer and ^{13}C spectra on a Brucker WH 90 spectrometer at 22.63 MHz using concentrated solutions in $CDCl_3$ alone or with DMSO-d_6. Chemical shifts are quoted in ppm downfield from TMS as internal standard. ^{13}C shifts were obtained using broad band decoupling; coupling information was obtained using gated decoupling techniques; symbols s, d, t, q and m have the usual connotations.
8. The numbering shown in structural formulae 2 and 4 is arbitrary and pertains to the acetylene dicarboxylic ester unit.
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11. Information obtained from a 90 MHz spectrum.

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