REACTIONS OF 2,1-BENZISOTHIAZOLES WITH ACETYLENIC ESTERS

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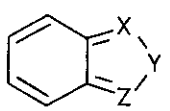
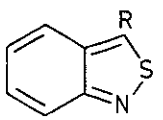
Abstract - 2,1-Benzisothiazole and the 3-methyl derivative react with dimethyl acetylenedicarboxylate (DMAD) under forcing conditions by addition across the hetero-diene and loss of sulphur to afford dimethyl quinoline-2,3-dicarboxylate and the corresponding 4-methyl derivative, respectively. Diethyl acetylenedicarboxylate and methyl propiolate react similarly but in very low yield. These reactions could involve initial Michael-type attack of the acetylenic ester on the heterocyclic nitrogen or concerted cycloaddition. 3-Amino-2,1-benzisothiazole and DMAD react differently to yield dimethyl 2-cyanoanilinofumarate, a possible mechanism is presented.

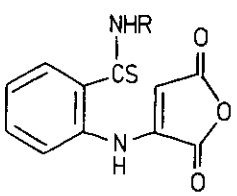
For many years there has been continued interest in cycloaddition reactions of ortho-quinonoid heterocycles. The high reactivity of standard dienophiles across the 1- and 3-positions of derivatives of structures (1)-(3) is well known.[1-3] In contrast, heterocycles (4)-(6) are far less reactive; they fail to add maleic anhydride,[4] and although dimethyl acetylenedicarboxylate (DMAD) does add to the N=C-C=N diene system of (5) and (6) reaction is sluggish.[5] Benzyne reacts with (5) and (6) quite differently yielding 1,2-benzisothiazole and 1,2-benzisoselenazole derivatives respectively.[5] 2,1-Benzisoxazole (7) reacts with N-phenylmaleimide[6] and benzyne[7] by addition of the dienophile to the hetero-diene; similar addition was claimed with maleic anhydride[8]



(1) X = Z = CH; Y = O
(2) X = Z = CH, Y = S
(3) X = Z = CH; Y = Se
(4) X = Z = N, Y = O
(5) X = Z = N; Y = S
(6) X = Z = N; Y = Se
(7) X = CH; Z = N; Y = O



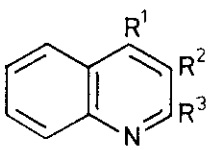
(8) a, R = H
b; R = Me
c; R = NH_2



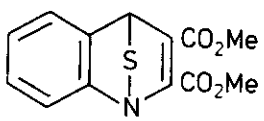
(9)

although since then Acheson and Poulter have reported negative results.[9] It has recently been shown that DMAD adds to (7) only when there is an electron-withdrawing group in the carbocyclic ring; thus derivatives of the 1,4-epoxy-1,4-dihydroquinoline ring system have been isolated.[10] Until now there has been only one report of reactions of dienophiles with 2,1-benzisothiazoles: the parent heterocycle (8a) and the 5-methoxy derivative fail to add maleic anhydride, whereas the 3-amino derivative gave N-(2,1-benzisothiazol-3-yl)-maleamic acid, and the 3-methylamino and 3-ethylamino analogues yielded (9, R = Me and Et) through a presumed further reaction of the maleamic acids.[11] We have found that (8a) does not react with N-phenylmaleimide, but we report reactions of 2,1- benzisothiazoles with acetylene carboxylic esters.

DMAD reacted with (8a) after heating at 90°C for 10 days to yield dimethyl quinoline-2,3-dicarboxylate (10a) in 5% yield. The 3-methyl derivative (8b) reacted with DMAD in refluxing xylene to afford the corresponding quinoline (10b) in significantly higher yield (23%). Attempts to obtain products from DMAD and 5-chloro- or 5-methoxy-2,1-benzisothiazole yielded intractable tars from which nothing could be obtained pure or crystalline. Both a concerted mechanistic pathway via (11), or a stepwise pathway via (12) are possible.



		R^1	R^2	R^3
(10)	a;	H	CO_2Me	CO_2Me
	b;	Me	CO_2Me	CO_2Me
	c;	H	CO_2Et	CO_2Et
	d;	Me	CO_2Et	CO_2Et
	e;	H	CO_2Me	H
	f;	H	H	CO_2Me



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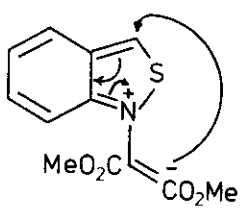
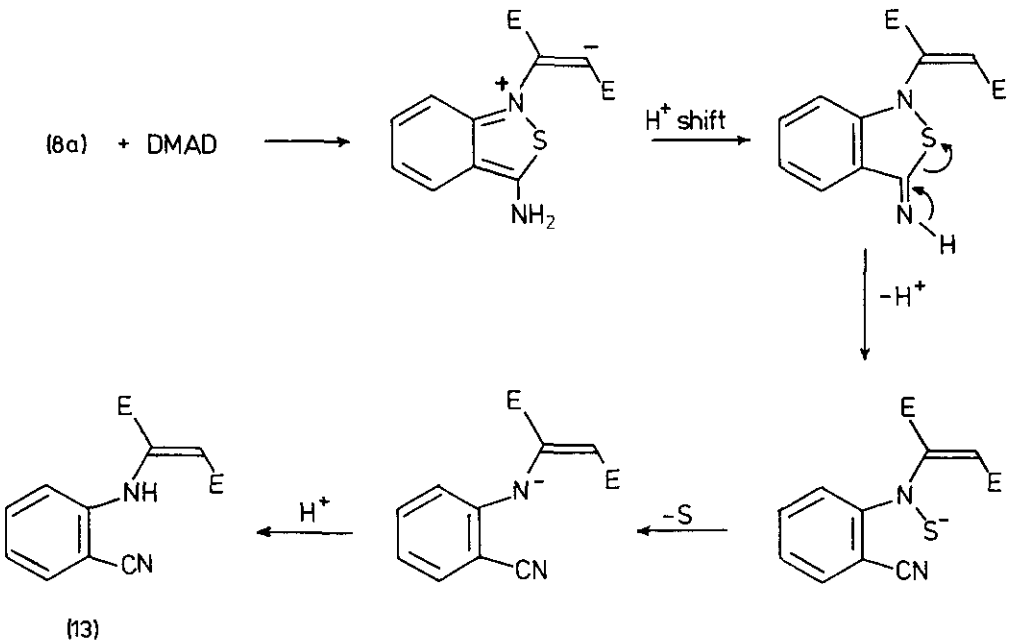


(12)

Reaction of diethyl acetylenedicarboxylate with (8a) and (8b) gave very low yields of quinolines (10c) and (10d) respectively. The addition of methyl propiolate to (8a) appears to be regiospecific as methyl quinoline-3-carboxylate (10e) (2%) was formed exclusively. Glc analysis of the crude reaction mixture by comparison with authentic (10e) and (10f) suggested that the 2-isomer (10f) was not present.

The addition of DMAD to 3-amino-2,1-benzisothiazole (8c) followed a different course. The yellow, crystalline product, $C_{13}H_{12}N_2O_4$ (a 1·1 adduct less sulphur) was formed in 56% yield and showed an ir absorption at 2220 cm^{-1} characteristic of an aromatic nitrile group, the ^1H nmr spectrum indicated one NH proton (δ 9.99), one vinylic proton (δ 5.69), and four ortho-coupled aromatic hydrogens (δ 7.64-6.20); the uv spectrum closely resembled that of dimethyl anilinofumarate.[12] *Taken together this evidence identifies the product as dimethyl 2-cyanoanilinofumarate* (or maleate). The chemical shifts for vinyl protons of the dimethyl anilinofumarates or maleates are very similar,[12,13] but the low field position of the NH proton is decisive[13] and enables the product to be unambiguously assigned the fumarate structure (13). The most likely mechanism of formation of (13) from (8c) and DMAD involves initial Michael-type attack of the acetylene on the heterocyclic nitrogen followed by a prototropic shift, ring opening, loss of sulphur, and gain of a proton as shown (Scheme).

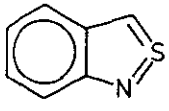


Scheme (E = CO_2Me)

Heindel et al[14] claim to have prepared dimethyl 2-cyanoanilinomaleate, although the formula given shows the fumarate structure, from 2-cyanoaniline and DMAD, but it is likely that this product is also the fumarate (13) in spite of a slight discrepancy in melting points. In both cases, the reaction conditions would be expected to yield the thermodynamically stable product, which for reactions between various anilines and DMAD is known to be the fumarate.[12] It was shown that under the present conditions (8c) does not initially decompose to 2-cyanoaniline which could then react with DMAD. It is interesting that the amino group of (8c) reacts at the carbonyl group of maleic anhydride, as is the case for most amines and even indole under the correct conditions,[15] while it attacks DMAD at the triple bond as is almost invariably the case with other amines.[16]

No products were obtained from reaction of DMAD with 2-methylamino- or 3-dimethylamino-2,1-benzisothiazole.

It is interesting to compare the moderate reactivity of (7) towards dienophiles with the reluctance of (8) to undergo similar reactions. Our observations of reaction of acetylene carboxylic esters with (8), albeit in low yields under forcing conditions, provide a rare example of addition to the hetero-ring of 2,1-benzisothiazoles, and if reaction is concerted, suggest that the ortho-quinonoid canonical form makes an important contribution to the overall structure of the ring system. Early evidence for a lack of ortho-quinonoid reactivity for (8) came from electrophilic substitution reactions,[17] and Davis and White postulated a contribution from canonical form (14) involving aromatisation of the benzenoid ring and participation of sulphur d orbitals. In support of this, nmr data and an X-ray structure of the 5-chloro-derivative indicated considerable π electron delocalisation throughout both rings.[18] However, the possibility of charged structures does not appear to be considered and canonical forms (15)-(17) may also contribute significantly to the stability of the ring system , although theoretical studies are needed to confirm this. It is noteworthy that both (5) and (8) are so much less reactive than (2) towards dienophiles.



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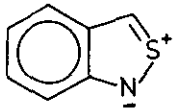

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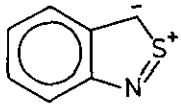

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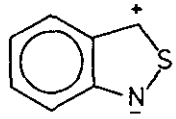

(17)

EXPERIMENTAL

Uv spectra were recorded on a Perkin Elmer 138 uv spectrophotometer. Mass spectra were recorded on an AEI MS 902 double-focussing spectrometer operating at an ionising energy of 70 eV. ^{1}H nmr spectra were recorded at 60 MHz on a Perkin-Elmer R-12 machine or at 100 MHz on a JEOL PFT 100 spectrometer; chemical shifts are quoted downfield from internal tetramethylsilane. Microanalyses were obtained on a Perkin Elmer 240 elemental analyser. Melting points were recorded on a Kofler micro-heating stage and are uncorrected. Column chromatography was performed on alumina Brockman activity II or Laporte Grade H 100-200 mesh. All chemicals were used as supplied unless otherwise stated. Acetonitrile, methanol and dioxan were distilled before use. Light petroleum refers to the fraction, b. p. 40-60°C.

Reaction of 2,1-Benzisothiazole (8a) with N-Phenylmaleimide - 2,1-Benzisothiazole (8a)[19] (1.35 g, 0.01 mole) and N-phenylmaleimide (1.73 g, 0.01 mole) were refluxed in xylene for 7 days, or heated together at 130°C for 24 h. After removal of solvent the ^{1}H nmr spectrum of the reaction mixture indicated no resonances other than those from starting materials.

Reaction of 2,1-Benzisothiazole (8a) with DMAD - A mixture of (8a) (0.67 g, 0.005 mol) and DMAD (0.71 g, 0.005 mol) was heated neat at 90°C for 240 h. The mixture was cooled and chromatographed on alumina; light petroleum-ether (9:1 v/v) eluted unchanged (8a) (0.11 g, 16%) followed by dimethyl quinoline-2,3-dicarboxylate (10a) (66 mg, 5%), white needles, mp 107-108°C (from methanol) (lit.,[20] 107-108°C). Found C, 63.41; H, 4.41, N, 5.38. $C_{13}H_{11}NO_4$ requires C, 63.67; H, 4.49; N, 5.71%); m/e 245 (M^+), identical by ir with that reported for (10a).[21] The same product was obtained under the following conditions. (8a) (1.35 g, 0.01 mole) and DMAD (1.42 g, 0.01 mole) were refluxed for 48 h in toluene (50 ml). After removal of solvent the ^{1}H nmr spectrum of the residue indicated no reaction had occurred. The residue was set aside at room temperature for 7 months after which time chromatography separated (10a) (37 mg, 2%). No reaction was observed after refluxing (8a) (1.35 g, 0.01 mole) and DMAD (1.42 g, 0.01 mole) in xylene (50 ml) for 168 h.

Reaction of 3-Methyl-2,1-benzisothiazole (8b) with DMAD - A solution of (8b)[19] (1.49 g, 0.01 mole) and DMAD (1.42 g, 0.01 mole) in xylene (30 ml) was refluxed for 245 h. Solvent was removed in vacuo and the resulting tar chromatographed on alumina. Light petroleum-ether (9:1 v/v) returned (8b) (0.45 g, 33%) followed by dimethyl 4-methylquinoline-2,3-dicarboxylate (10b) (0.59 g, 23%), white needles (from hexane), m p 98-99°C. Found: C, 64.99, H, 5.21; N 5.19. $C_{14}H_{13}NO_4$ requires C, 64.86; H, 5.02; N, 5.40%, m/e 259 (M^+); $\delta_H(CCl_4)$ 8.2-7.4 (4H, m, Ar-H), 3.96 (3H, s, CO_2Me), 3.88 (3H, s, CO_2Me), 2.60 (3H, s, 4-Me).

When a mixture of (8b) (0.74 g, 0.005 mole) and DMAD 1.42 g, 0.01 mole) was heated neat at 100°C for 7 days an intractable tar was formed.

Reaction of 2,1-Benzisothiazole (8a) with Diethyl Acetylenedicarboxylate - The ester (0.85 g, 0.005 mole) and (8a) (0.67 g, 0.005 mole) were heated together at 90°C for 10 days. The mixture was adsorbed onto chromatographic alumina, made into a column and eluted with light petroleum-ether (9:1 v/v). First fractions contained unreacted (8a) (0.18 g, 22%). Light petroleum-ether (8:2 v/v) eluted diethyl quinoline-2,3-dicarboxylate (10c) (0.02 g, 1%), buff needles, mp 54-56°C (from ethanol) (lit.,[20] 55°C). (Found: C, 65.71; H, 5.76; N, 5.40. $C_{15}H_{15}NO_4$ requires C, 65.93; H, 5.50; N, 5.13%, m/e 273 (M^+). Continued elution yielded red tars (ca. 300 mg) which contained (10c) (by nmr) but from which nothing could be obtained pure or crystalline.

Reaction of 3-Methyl-2,1-benzisothiazole (8b) with Diethyl Acetylenedicarboxylate - A mixture of (8b) (1.49 g, 0.01 mole) and the ester (1.70 g, 0.01 mole) was heated at 90°C for 10 days. The cooled mixture was added to an alumina column; light petroleum-ether (8:2 v/v) gave unchanged (8b) (0.20 g, 13%) followed by diethyl 4-methylquinoline-2,3-dicarboxylate (10d) (0.11 g, 4%), viscous yellow oil, bp 100°C/0.1 mm Hg (lit.,[21] 135°C/5 mm Hg) which partly solidified on standing. Found: C, 67.21; H, 5.70; N, 4.99. $C_{16}H_{17}NO_4$ requires C, 66.90; H, 5.92; N, 4.88%, m/e 287 (M^+).

Reaction of 2,1-Benzisothiazole (8a) with Methyl Propiolate - A mixture of (8a) (1.35, 0.01 mole) and methyl propiolate (0.84 g, 0.01 mole) was heated at 100°C for 10 days. The mixture was adsorbed onto alumina and chromatographed using light petroleum-ether (8:2 v/v) as eluent. First fractions were unchanged (8a) (0.27 g, 20%) followed by an orange oil which on chilling and trituration with ice-cold methanol afforded methyl quinoline-3-carboxylate (10e) (0.04 g, 2%) mp 74-75°C (lit.,[22] 76°C) (identical by glc, nmr and ir with an authentic sample prepared from esterification of quinoline-2,3-dicarboxylic acid under conditions reported to give the diester.[21]) Found: C, 70.20; H, 4.71; N, 7.71. $C_{11}H_9NO_2$ requires C, 70.59; H, 4.81; N, 7.49%, m/e 187 (M^+); $\delta_H(CDCl_3)$ 9.24 (d, 1H, H_2, J_{24} 2.5 Hz, confirmed by double resonance), 8.81 (d, 1H, H_4, J_{24} 2.5 Hz), 8.2-7.5 (m, 4H, Ar-H), 5.96 (s, 3H, CO_2Me). Glc analysis of the crude reaction mixture showed the absence of isomer (10f) by comparison of retention times with an authentic sample [prepared from quinoline-2-carboxylic acid and diazomethane in 93% yield, mp 81-82°C (from light petroleum) lit.,[23] 86°C]

Reaction of 3-Amino-2,1-benzisothiazole (8c) with DMAD - Compound (8c)[24] (0.75 g, 5.0 mmole) and DMAD (0.71 g, 5 mmol) were heated neat at 100°C for 24 h. The mixture was cooled and the resulting tar was chromatographed on an alumina column with chloroform as eluent. The first fraction afforded dimethyl 2-cyanoanilinofumarate (13) (0.73 g, 56%) mp 111-114°C (lit.,[14] 105-106°C) after recrystallisation from toluene. Found. C, 60.27; H, 4.81. N, 10.4; $C_{13}H_{12}N_2O_4$

requires C, 60.00; H, 4.61; N, 10.8%; m/e 260 (M^+, 24), 228(18), 201(13), 200(16), 170(15), 169(100), 141(10), 114(10), 102(16), 28(27); λ_{max}(MeOH) 218, 330 nm (ε 2.60 x 10^4, 1.62 x 10^4); ν_{max} (nujol) 3240 w sh, 3195 w, 2220, 1669, 1639, 1599, 1577, 1503, 1438, 1298, 1280, 1248, 1227, 1184, 1137, 1093, 1021, 959 cm^{-1}; $\delta_H(CDCl_3)$ 9.99 (NH, deuterium exchangeable), 7.64-6.20 (m, 4H, ArH), 5.69 (s, 1H, C=CH), 3.74 and 3.71 (each s, 3H, CO_2Me).

No products could be isolated from reaction of DMAD with 3-methylamino-,[24] 3-dimethylamino-,[24] 5-chloro-[18] or 5-methoxy-2,1-benzisothiazole.[20] In all cases intractable tars resulted.

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