(1965).
(18) E. g., see C. H. Depuy, M. Isaks, K. Eilors, and G. F. Morris, *J. Org. Chem.*, **29**, 3503 (1964).
(19) Aldrich Chemical Co. No. V-260-7.
(20) There is a broad, ill-defined peak centered at this value and it is assumed to be due to the intramolecularly H-bonded OH. The oily product obtained from acetylation of **5c** shows the following spectroscopic properties: IR ($CHCl_3$) 1735 and 1775 cm^{-1}; NMR ($CDCl_3$) δ 7.61 (s, 1 H, aromatic H ortho to OCOMe and COOMe), 7.25–6.60 (m, 10 H, aromatic), 3.52 (s, 3 H, $COOCH_3$), 3.44 (s, 3 H, $COOCH_3$), 2.28 (s, 3 H, $OCOCH_3$).
(21) The shift in the ester carbonyl stretching frequency to a lower value is likely due to intramolecular H bonding with the hydroxyl group: e.g., see F. Dalton, J. I. McDougall, and G. D. Meakins, *J. Chem. Soc.*, 4069 (1963); A. R. H. Cole and G. T. A. Muller, *ibid.*, 1224 (1959).
(22) R. G. Harvey, S. W. Goh, and C. Cortez, *J. Am. Chem. Soc.*, **97**, 3468 (1975).

Reaction of 2-Aminobenzazoles with Dimethyl 2-Aminofumarate. Synthesis and Nuclear Magnetic Resonance Spectroscopy of 4-Oxopyrimido[2,1-*b*]benzazoles

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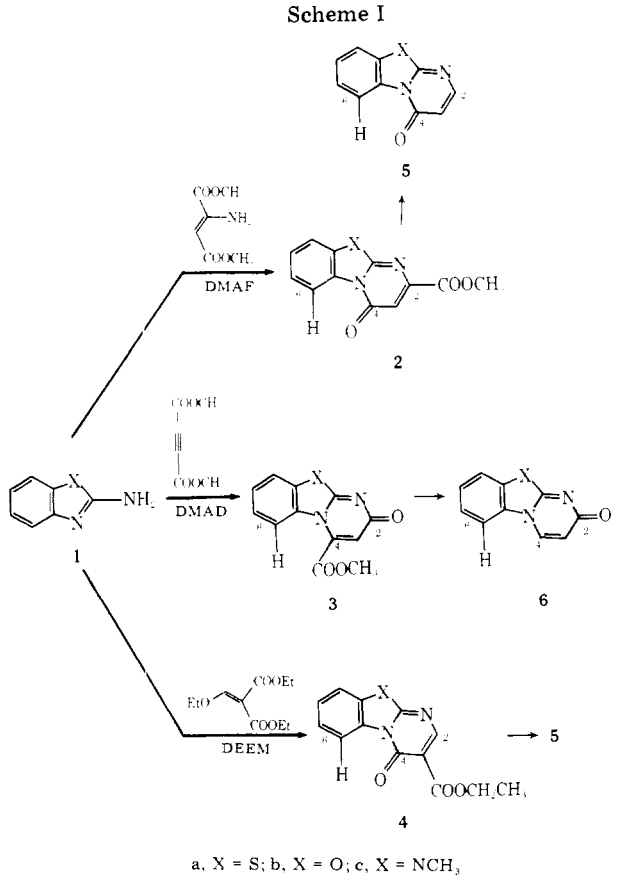
A convenient and apparently general procedure has been developed to prepare 4-oxopyrimido[2,1-*b*]benzazole-2-carboxylates by reaction of dimethyl 2-aminofumarate (DMAF) with 2-aminobenzothiazole, 2-aminobenzoxazole, or 2-amino-1-methylbenzimidazole. This new method complements the reaction of dimethyl acetylenedicarboxylate (DMAD) with these 2-aminobenzazoles since their reaction with DMAD gives the isomeric 2-oxopyrimido[2,1-*b*]benzazole-4-carboxylates. The esters derived from DMAF were hydrolyzed and decarboxylated to compounds which were identical with those obtained by hydrolysis and decarboxylation of the esters produced by reaction of each of the 2-aminobenzazoles with diethyl ethoxymethylenemalonate (DEEM). These decarboxylated derivatives are distinctly different from those obtained by hydrolysis and decarboxylation of the DMAD-derived esters. The assignments of compounds as 2-oxo or 4-oxo products were made on the basis of the ^1H NMR spectra, specifically by reference to the chemical shift of the absorbance assigned to the C-6 benzo ring proton.

During the course of a medicinal chemical project in our laboratories, we became interested in preparing compounds of structure **2** (Scheme I), where X = S, O, or NCH_3. Theoretically, such compounds might be available by Michael reaction of a 2-aminobenzazole **1** with dimethyl acetylenedicarboxylate (DMAD) at the 2-amino group, followed by cyclization onto the ring nitrogen. However, since the ring nitrogen is also a potential nucleophilic site for the initial Michael reaction, the possibility exists that the reaction will give the 2-oxo structure **3** rather than the 4-oxo structure **2**, which we desired.

Scheme I



a, X = S; b, X = O; c, X = NCH_3

A literature survey indicated that the reaction of DMAD with 2-aminobenzothiazole has been more thoroughly investigated than its reaction with the other 2-aminobenzazoles, and it seemed likely that, at least for this case, the usual product is in fact the 2-oxo isomer **3a**. This structure has been assigned on the basis of ^1H NMR data, including comparison with ^1H NMR data of compounds which have the 4-oxo structure but which do not have the ester functionality as in **2**.[1,2] Reimlinger et al., in a brief report, have described the reaction of **1a** with DMAD under various reaction conditions, one of which gave a chromatographically separable mixture of **2a** and **3a** which was isolated in yields of 2 and 6%, respectively.[3] The authors did not discuss the basis for their structural assignments. Finally, in a report which appeared after the commencement of our work, the structure of **3a** was established unequivocally by X-ray crystallography.[4]

The reaction of 2-aminobenzoxazole (**1b**) with DMAD has been reported to give **3b** rather than **2b**, and again the structure assignment is based on ^1H NMR evidence.[2] Reaction of 2-amino-1-methylbenzimidazole (**1c**) with DMAD has not been reported, although the reaction of 2-aminobenzimidazole (**1**, X = NH) apparently also gives a tricyclic compound of the 2-oxo (**3**) rather than 4-oxo (**2**) structure.[2] No X-ray analyses have been reported in these cases; ^1H NMR data for the products, and for related but not isomeric compounds, were the basis for structural assignments.

At the time our work began we felt that the published

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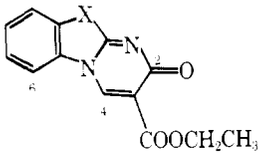
structural evidence, though compelling, was not definitive, especially since, with the exception of the one benzothiazole report by Reimlinger,[3] only one of the two possible isomers **2** and **3** was available for comparison. We now wish to report a general synthetic method for preparing compounds of structure **2** and the use of these compounds and their isomers and derivatives to satisfactorily define their structures and the structures of the DMAD-derived isomers.

We first set out to prove to our own satisfaction that the reactions of DMAD with the three 2-aminobenzazoles **1a–c** give, in each case, compounds of structure **3** rather than **2.** A possible approach to this problem was suggested to us by the work of Dunwell and Evans on the benzothiazole case[1] and by the work of Chow et al. on the reaction of diethyl ethoxymethylenemalonate (DEEM) with 2-aminobenzimidazole.[5] This approach focused on the chemical shift of the C-6 proton in the ^{1}H NMR spectra of these compounds. If the tricyclic compounds under consideration have the 4-oxo structure as in **2,** one would expect the C-6 proton to be shifted downfield from the main aromatic signals by the paramagnetic anisotropic effect of the carbonyl at C-4. This is indeed the case for the products of the reaction of DEEM with 2-aminobenzothiazole,[1,2,6] 2-aminobenzoxazole,[2] and 2-aminobenzimidazole,[2,5] although a similar reaction with 2-amino-1-methylbenzimidazole has not been reported. The structural assignments for the DEEM-derived products were made by the previous workers on the basis of the downfield shift of the C-6 proton since one would not expect such a shift for compounds having the alternative structure **7.**



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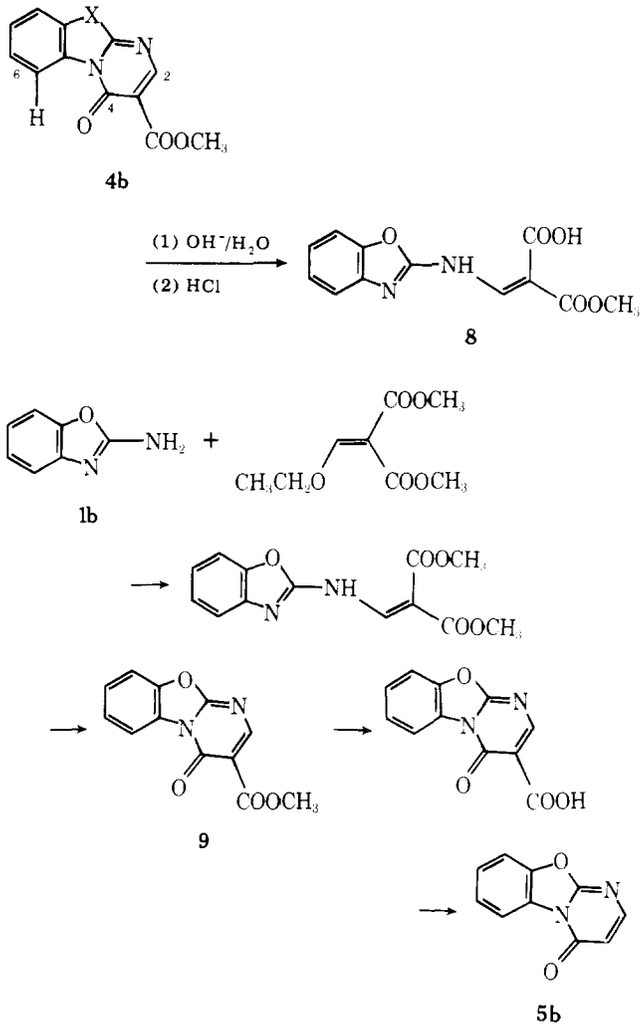
This analysis seemed reasonable in the case of these DEEM-derived products, but its extension to the DMAD-derived structure assignment seemed more ambiguous to us since it is unclear what effect the C-4 carbomethoxy in structure **3** might have on the chemical shift of the C-6 proton. This problem seemed especially ambiguous to us at the outset if only one of the two possible isomers **2** or **3** was actually available for spectral analysis. Reimlinger et al.[3] did isolate both isomers from 2-aminobenzothiazole, and their reported ^{1}H NMR data are consistent with the expectation that an aromatic absorbance would be shifted downfield for the 4-oxo compound, but they assigned this absorbance to the C-9 proton, which seemed incorrect to us.

We therefore decided to submit the DMAD- and DEEM-derived esters to hydrolysis and subsequent decarboxylation in order to observe the resulting chemical shift differences for the C-6 proton. We reasoned that if the actual structures of the DMAD-derived esters and the DEEM-derived esters were **3** and **4,** respectively, as suggested by the previous workers, then the C-6 proton chemical shift should remain about the same after decarboxylation of **4,** but should shift one way or another after decarboxylation of **3.** Furthermore, if the structures were as suggested, then the decarboxylation products should be distinctly different from each other; if the decarboxylation products were identical, one of the structure assignments must be wrong.

The DMAD-derived esters were prepared and saponified by aqueous base. The resulting acids were decarboxylated by brief thermolysis in refluxing diphenyl ether or by heating them in quinoline in the presence of copper powder. The DEEM-derived esters **4a** and **4c** were prepared and saponified by aqueous base, but the resulting acids would not decarboxylate in refluxing diphenyl ether. The acids did smoothly

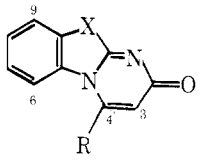
Scheme II



decarboxylate, however, by using the copper powder in quinoline method. The benzoxazole-derived ester **4b** behaved differently upon treatment with base; 1 equiv of base resulted in cleavage of the amide bond and therefore ring opening to **8** (Scheme II) rather than hydrolysis of the ester. Attempts to obtain the tricyclic acid by ring closure of **8,** by saponification with 2 equiv of base followed by ring closure, or by acid hydrolysis of the ester were unsuccessful. The acid was finally obtained by LiI/pyridine cleavage of the methyl ester **9,** which was made from dimethyl ethoxymethylenemalonate[7] and 2-aminobenzoxazole. Decarboxylation of the acid was then readily accomplished by heating it, in quinoline, in the presence of copper powder.

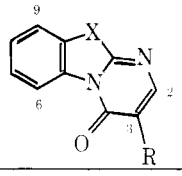
The ^{1}H NMR data for the decarboxylation products (Tables I and II) bear out the structure assignments of the previous workers. First of all, it should be noted that the DEEM-derived decarboxylation products **5** are indeed different from the DMAD-derived ones **6.** Secondly, the relative chemical shifts of the C-6 proton absorbances should be noted. These chemical shifts can be assigned by considering that although within a series (e.g., **3a, 4a, 5a,** and **6a**) the C-9 and C-6 proton signals appear similar in multiplicity (each is a doublet of doublets with J values of ~8 and 1–3 Hz), the C-9 proton chemical shifts should be relatively invariant. The C-6 proton, in contrast, is in a position to be affected by the proximity of the functionality at C-4, and some variation in its chemical shift within a series of compounds is therefore expected. Such a variation is in fact observed. Thus, within a series (where X = S, for example) a variation of as much as

Table I. ^{1}H NMR Data for DMAD-Derived Products, δ



compd	X	R	3-H	4-H	6-H	7,8-H	9-H
3a	S	$COOCH_3$	6.67		7.57	7.4–7.5	8.05
3b	O	$COOCH_3$	6.75		7.77	7.4–7.5	7.81
3c	NCH_3	$COOCH_3$	6.59		7.7	7.3–7.5	7.7
6a	S	H	6.33	8.85	8.0	7.5–7.6	8.0
6b	O	H	6.33	8.73	7.95	7.5	7.75
6c	NCH_3	H	6.13	8.61	7.89	7.3–7.4	7.58

Table II. ^{1}H NMR Data for DEEM-Derived Products, δ



compd	X	R	2-H	3-H	6-H	7,8-H	9-H
4a	S	COOEt	8.61		8.98	7.6–7.7	8.15
4b	O	COOEt	8.70		8.35	7.6	7.90
4c	NCH_3	COOEt	8.73		8.56	7.5–7.7	7.80
5a	S	H	8.07	6.45	8.97	7.6	8.10
5b	O	H	8.06	6.39	8.28	7.5–7.6	7.81
5c	NCH_3	H	8.05	6.09	8.51	7.4–7.6	7.72
8[a]	O	$COOCH_3$	8.73		8.39	7.5	7.5

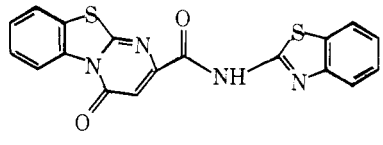
[a] The spectrum was measured in $CDCl_3$.

1.4 ppm is observed for the C-6 proton chemical shift, while the C-9 proton variation is only 0.15 ppm.

As Table I indicates, the position of the C-6 proton absorbance in the DMAD-derived products has shifted downfield after hydrolysis and decarboxylation, suggesting that the ester functionality was in a position to affect the C-6 proton chemical shift. This information supports the 2-oxo structural assignment **3.** As expected, there is very little change in the C-6 proton chemical shift after hydrolysis and decarboxylation of the DEEM-derived esters **4,** as shown in Table II. Finally, the fact that the DEEM-derived decarboxylation products show a downfield shift of the C-6 proton signal of about 0.3–1.0 ppm compared to the isomeric DMAD-derived decarboxylation products provides confirmation of the structure assignments without the potentially confusing influence of ester functionalities.

To make this analysis more complete, however, we wanted to find a general method to prepare compounds of structure **2** so that they and their decarboxylated derivatives would be available for comparison. Reaction of diethyl oxaloacetate with a 2-aminobenzazaole seemed to be a possible alternative procedure which might lead to structure **2.**[8] However, we were unable to obtain any products from such a reaction, nor could we obtain a useful reaction between 2-aminobenzothiazole and dimethyl 2-methoxyfumarate.[9] Since it has been reported that ethyl 3-aminocrotonate is superior to ethyl acetoacetate in similar condensation reactions with cyclic amidines,[10] we thought that the analogous reagent, dimethyl 2-aminofumarate (DMAF), might be useful for our needs. DMAF is readily available by condensation of ammonia with dimethyl acetylenedicarboxylate.[11] We soon found that reaction of DMAF with 2-aminobenzothiazole, 2-aminobenzoxazole, and 2-amino-1-methylbenzimidazole gives reasonable yields of new compounds which are isomeric with, but distinctly different from, the esters obtained by reaction of the same aminobenzazoles with DMAD.

These new esters, which were eventually assigned structure **2,** were obtained by heating the starting amine at about 160 °C in the presence of ~3 equiv of DMAF. After a workup which sometimes involved a rapid column chromatography, the esters were isolated in yields of 24, 49, and 46%, respectively, from amines **1a, 1b,** and **1c.** In the case of **2a,** we were unable to increase the yield by variations of time, temperature, ratio of reagents, use of various solvents, and acid or base catalysis. A major byproduct was isolated from this reaction, which proved to be the amide **10,**[12] derived presumably by



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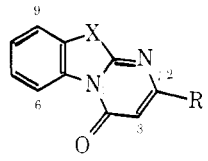
addition of DMAF and cyclization to the tricyclic ester **2a** followed by reaction with unreacted starting amine to give the amide. This amide can theoretically be hydrolyzed to the corresponding acid, but several attempts to effect such a hydrolysis were unsuccessful.

Saponifications of **2** were readily accomplished by hydrolysis with an equivalent of base followed by acidification. The acids derived from 2-aminobenzothiazole and 2-amino-1-methylbenzimidazole were decarboxylated by thermolysis in diphenyl ether; the 4-oxopyrimido[2,1-*b*]benzoxazole-2-carboxylic acid would not decarboxylate under these conditions, but did decarboxylate using the copper powder/quinoline method.

The DMAF-derived decarboxylation products were identical with the DEEM-derived decarboxylation products, as

Table III. ^{1}H NMR Data for DMAF-Derived Products, δ



compd	X	R	2-H	3-H	6-H	7,8-H	9-H
2a	S	$COOCH_3$		6.93	8.92	7.6	8.12
2b	O	$COOCH_3$		6.97	8.31	7.55–7.65	7.86
2c	NCH_3	$COOCH_3$		6.65	8.52	7.6–7.7	7.76
5a	S	H	8.07	6.45	8.97	7.6	8.1
5b	O	H	8.06	6.39	8.28	7.5–7.6	7.81
5c	NCH_3	H	8.02	6.05	8.47	7.4–7.5	7.65

indicated by the infrared and ^{1}H NMR spectral data, as well as by the mixture melting points. The ^{1}H NMR data show for each of the esters **2** (Table III) a downfield shift of the C-6 proton absorbance from the rest of the aromatic signals. The position of this downfield chemical shift does not appreciably change after decarboxylation, indicating that the ester functionality is not in a position to affect the C-6 proton and thus verifying the 4-oxo structure **2** assigned to the esters. Thus, all of the ^{1}H NMR data tie together nicely to substantiate the structural assignments.

We speculate that the formation of **2** results from an initial enamine exchange reaction of the heterocyclic amine with DMAF,[13] followed by ring closure onto the ring nitrogen. This reaction is thus in contrast to that with DMAD, which involves initial Michael condensation of the ring nitrogen, followed by ring closure with the free amine. The use of this DMAF reaction to prepare compounds of potential therapeutic use will be the subject of future reports from these laboratories.

Experimental Section

Melting points were obtained with a Mel-Temp block or a Uni-melt apparatus and are uncorrected. The IR spectra were obtained, using Nujol mulls, on a Perkin-Elmer Infracord spectrophotometer. The ^{1}H NMR spectra were measured in Me_2SO-d_6, unless otherwise stated, using a Varian XL-100 or T-60 spectrometer and are reported in parts per million (δ) downfield from tetramethylsilane. Microanalyses were performed by J. H. Gagnon and co-workers in the Central Research Analytical Group, 3M Co.

Methyl 4-Oxopyrimido[2,1-*b*]benzothiazole-2-carboxylate (2a). Portionwise addition of 2-aminobenzothiazole (15.0 g, 0.100 mol) to dimethyl 2-aminofumarate (DMAF)[7] (45 g, 0.28 mol), while heating at 160 °C under a stream of nitrogen, was carried out over 10 min. Heating at 160 °C was continued for 3 h, and the mixture was allowed to cool and then suspended in 100 mL of methanol. The solid was filtered and suspended in 300 mL of chloroform. The resulting suspension was filtered to remove the amide byproduct **10**.[12] The filtrate was concentrated in vacuo, and the residue was chromatographed on 200 g of silica gel, eluting with 1 L of benzene and then 10% ethyl acetate in benzene, collecting 250-mL fractions. The bulk of the desired product was eluted in fractions 4–7, which were combined and concentrated in vacuo to 6.23 g (24%) of solid: mp 199–200 °C (lit.[3] mp 202–204 °C); IR 5.70, 5.88 μm.

Anal. Calcd for $C_{12}H_8N_2O_3S$: C, 55.4; H, 3.1; N, 10.8. Found: C, 55.0; H, 3.0; N, 10.8.

Methyl 4-Oxopyrimido[2,1-*b*]benzoxazole-2-carboxylate (2b). A mixture of 2-aminobenzoxazole[14] (20.0 g, 0.149 mol) and DMAF (70 g, 0.44 mol) was heated at 160 °C under a stream of nitrogen for 6 h. The mixture was cooled and chromatographed on a Florisil column, eluting first with chloroform and then 50% ethyl acetate in chloroform to obtain 16.6 g (46%) of solid: mp 175–177 °C; IR 5.78, 5.88 μm.

Anal. Calcd for $C_{12}H_8N_2O_4$: C, 59.0; H, 3.3; N, 11.5. Found: C, 58.8; H, 3.3; N, 11.4.

Methyl 10-Methyl-4-oxopyrimido[2,1-*b*]benzimidazole-2-carboxylate (2c). A mixture of 2-amino-1-methylbenzimidazole[15] (5.0 g, 0.034 mol) and DMAF (16 g, 0.10 mol) was heated at 140 °C under a nitrogen stream for 2 h. The mixture was allowed to cool and suspended in 100 mL of methanol, and the solid was filtered to give 4.26 g (49%) of **2c**, mp 233–234 °C. An analytical sample was prepared by recrystallization from ethanol/chloroform: mp 233–234 °C; IR 5.73, 5.87 μm.

Anal. Calcd for $C_{13}H_{11}N_3O_3$: C, 60.7; H, 4.3; N, 16.4. Found: C, 60.7; H, 4.3; N, 16.8.

Methyl 2-Oxopyrimido[2,1-*b*]benzothiazole-4-carboxylate (3a). A mixture of 2-aminobenzothiazole (5.00 g, 33.3 mmol) and dimethyl acetylenedicarboxylate (DMAD) (6.00 g, 42.2 mmol) in 100 mL of methanol was refluxed overnight. The reaction mixture was cooled to precipitate a solid which was collected by filtration to yield 5.74 g (59%) of **3a:** mp 192–193 °C (lit. mp 192–195,[3] 203,[2] and 183–185 °C[4]); IR 5.74, 6.00 μm.

Anal. Calcd for $C_{12}H_8N_2O_3S$: C, 55.4; H, 3.1; N, 10.8. Found: C, 55.4; H, 2.9; N, 10.8.

Methyl 2-Oxopyrimido[2,1-*b*]benzoxazole-4-carboxylate (3b). Use of 2-aminobenzoxazole in the above procedure gave a 70% yield of **3b:** mp 202–204 °C (lit.[2] mp 207 °C); IR 5.70, 6.05 μm.

Anal. Calcd for $C_{12}H_8N_2O_4$: C, 59.1; H, 3.3; N, 11.5. Found: C, 58.7; H, 3.2; N, 11.5.

Methyl 10-Methyl-2-oxopyrimido[2,1-*b*]benzimidazole-4-carboxylate (3c). Use of 2-amino-1-methylbenzimidazole in the above procedure gave a 66% yield of **3c:** mp 247–248 °C; IR 5.72, 6.08 μm.

Anal. Calcd for $C_{13}H_{11}N_3O$: C, 60.7; H, 4.3; N, 16.3. Found: C, 60.4; H, 4.2; N, 16.4.

Ethyl 4-Oxopyrimido[2,1-*b*]benzothiazole-3-carboxylate (4a). A mixture of 2-aminobenzothiazole (8.83 g, 58.8 mmol) and diethyl ethoxymethylenemalonate (DEEM) (14.0 g, 64.8 mmol) in 150 mL of ethanol was refluxed overnight. The mixture was cooled, and the solid was collected by filtration to yield 15.7 g (83%) of the intermediate diester, mp 103.5–105.5 °C (lit.[2] mp 109 °C). This diester (15.0 g, 46.9 mmol) in 250 mL of diphenyl ether was heated at 250 °C in an open flask for 90 min. The reaction mixture was allowed to cool, diluted with 750 mL of hexane, and cooled overnight to precipitate a solid. Collection by filtration and recrystallization (charcoal) from DMF gave 5.56 g (43%; 36% overall) of **4a:** mp 140–143 °C (lit. mp 147,[2] 142–143,[1] and 136–138 °C[8]); IR 5.78, 5.90 μm.

Anal. Calcd for $C_{13}H_{10}N_2O_3S$: C, 56.9; H, 3.7; N, 10.2. Found: C, 56.7; H, 3.6; N, 10.2.

Ethyl 4-Oxopyrimido[2,1-*b*]benzoxazole-3-carboxylate (4b). Use of 2-aminobenzoxazole in the above procedure gave first the intermediate diester (after 3 days reflux) in 79% yield, mp 105–107 °C (lit.[2] mp 105–107 °C). Cyclization of this diester in diphenyl ether as above gave an 82% yield (65% overall) of **4b:** mp 151–153 °C (ethanol) (lit.[2] mp 158 °C); IR 5.80 μm.

Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.5; H, 3.9; N, 10.9. Found: C, 60.4; H, 3.9; N, 10.9.

Ethyl 10-Methyl-4-oxopyrimido[2,1-*b*]benzimidazole-3-carboxylate (4c). A mixture of 2-amino-1-methylbenzimidazole (3.00 g, 20.4 mmol) and DEEM (4.50 g, 20.8 mmol) in 50 mL of methanol was refluxed for 15 min. The reaction mixture was cooled, and the solid was collected by filtration to yield 3.50 g (63%) of the cyclized product **4c:** mp 189–190 °C; IR 5.71, 6.00 μm.

Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 62.0; H, 4.8; N, 15.5. Found: C, 61.7; H, 4.7; N, 15.8.

4-Oxopyrimido[2,1-*b*]benzothiazole (5a). From DEEM-Derived Ester 4a. A mixture of **4a** (9.00 g, 32.8 mmol) and NaOH (1.4 g, 35 mmol) in 800 mL of water was warmed at 60 °C overnight. The reaction mixture was filtered, and the filtrate was acidified with concentrated HCl to precipitate a white solid which was collected by filtration, washed with water, and dried to yield 4.95 g (61%) of 4-oxopyrimido[2,1-*b*]benzothiazole-3-carboxylic acid: mp 230–232 °C dec; IR 5.70, 6.04 μm.

This acid (1.53 g, 6.22 mmol) was taken up in 25 mL of quinoline, ~0.5 g of copper powder was added, and the mixture was heated at 200 °C for 45 min. The hot mixture was filtered to remove the copper, and the quinoline was removed by distillation at reduced pressure. The residue was suspended in 150 mL of hot benzene and filtered to remove insoluble material. The hot filtrate was treated with charcoal, filtered, and concentrated in vacuo. The residue was recrystallized (charcoaled) from benzene to give 0.23 g (18%) of **5a:** mp 163–164 °C (lit.[1] mp 168 °C); IR 5.90 μm.

Anal. Calcd for $C_{10}H_6N_2OS$: C, 59.4; H, 3.0; N, 13.9. Found: C, 59.6; H, 2.9; N, 13.8.

From DMAF-Derived Ester 2a. A mixture of **2a** (1.30 g, 5.00 mmol) and NaOH (0.30 g, 7.5 mmol) in 70 mL of water was heated at 70 °C overnight, by which time all solids had dissolved. The solution was cooled and acidified with concentrated HCl to precipitate a solid which was collected by filtration, washed with water, and dried to give 0.69 g (56%) of 4-oxopyrimido[2,1-*b*]benzothiazole-2-carboxylic acid: mp 261–263 °C dec; IR 5.74 (sh), 5.87 μm.

This acid (0.63 g, 2.54 mmol) was refluxed in 15 mL of diphenyl ether for 45 min. The reaction mixture was cooled, diluted to 50 mL with hexane, and cooled in an ice bath to precipitate a solid which was collected by filtration and recrystallized (charcoaled) from benzene to give 0.16 g (31%) of **5a:** mp 160–162 °C; mixture melting point with the product obtained from **4a,** 161–163 °C; IR 5.92 μm. The ^1H NMR data (Tables II and III) also indicate that the two compounds are identical.

4-Oxopyrimido[2,1-*b*]benzoxazole (5b). From Dimethyl Ethoxymethylenemalonate-Derived Ester 9. A mixture of **9** (5.0 g, 21 mmol) and LiI (7.0 g, 52 mmol) in 20 mL of pyridine was refluxed under a nitrogen atmosphere overnight. The reaction mixture was concentrated in vacuo, and the residue was dissolved in 300 mL of water. This solution was acidified with concentrated HCl to precipitate a solid which was collected by filtration, washed with water, and dried to give 1.5 g (32%) of 4-oxopyrimido[2,1-*b*]benzoxazole-3-carboxylic acid: mp 268–270 °C dec; IR 5.75, 6.00, 6.12 (sh) μm.

A mixture of this acid (1.03 g, 4.48 mmol) and ~0.2 g of copper powder in 25 mL of quinoline was heated at 200 °C for 1 h and then cooled and filtered to remove the copper. The quinoline was removed by distillation at reduced pressure, and the residue was taken up in 100 mL of hot benzene and filtered to remove insoluble material. The filtrate was concentrated in vacuo. The residue was triturated with ether and the solid was collected by filtration to give 0.17 g (20%) of **5b.** Recrystallization (charcoal) from benzene/hexane gave an analytical sample: mp 150–151 °C; IR 5.85, 6.10, 6.23 μm.

Anal. Calcd for $C_{10}H_6N_2O_2$: C, 64.5; H, 3.2; N, 15.1. Found: C, 64.4; H, 3.0; N, 15.0.

From DMAF-Derived Ester 2b. A mixture of **2b** (3.50 g, 14.4 mmol) and NaOH (0.65 g, 16 mmol) in 100 mL of water was warmed to 70 °C, by which time all of the solids had dissolved. The mixture was allowed to come to room temperature and filtered; the filtrate was cooled and acidified with concentrated HCl to precipitate a solid which was collected by filtration, washed with water, and dried to give 2.15 g (65%) of 4-oxopyrimido[2,1-*b*]benzoxazole-2-carboxylic acid: mp 280–281 °C dec; IR 5.64, 5.93, 6.05 (sh), 6.20 μm.

A mixture of this acid (1.13 g, 4.90 mmol) and ~0.5 g of copper powder in 25 mL of quinoline was heated to 190 °C and maintained at this temperature for 45 min. The hot mixture was filtered to remove the copper, and the filtrate was concentrated by removal of the quinoline by distillation at reduced pressure. The residue was taken up in 150 mL of hot chloroform, treated with charcoal, and filtered. The filtrate was concentrated in vacuo. The residue was recrystallized (charcoaled) from benzene/hexane to give 0.07 g (8%) of **5b:** mp 148.5–150 °C; mixture melting point with the material obtained from **9,** 148.5–150 °C; IR 5.85; 6.10, 6.23 μm. The ^1H NMR data (Tables II and III) also indicate that the two compounds are identical.

10-Methyl-4-oxopyrimido[2,1-*b*]benzimidazole (5c). From DEEM-Derived Ester 4c. Use of **4c** in the procedure described above to prepare **5a** from **4a** gave first a 93% yield of 10-methyl-4-oxopyrimido[2,1-*b*]benzimidazole-3-carboxylic acid: mp 345–348 °C dec; IR 5.80, 6.05, 6.30 μm. From this acid, using the Cu/quinoline procedure, was obtained a 52% yield of **5c:** mp 188–189 °C; IR 5.87, 6.14 (sh), 6.25 μm.

Anal. Calcd for $C_{11}H_9N_3O$: C, 66.4; H, 4.5; N, 21.1. Found: C, 66.2; H, 4.5; N, 20.9.

From DMAF-Derived Ester 2c. Use of **2c** in the procedure described above to prepare **5a** from **2a** gave first in 78% yield, 10-methyl-4-oxopyrimido[2,1-*b*]benzimidazole-2-carboxylic acid: mp 274–275 °C dec; IR 5.80, 6.00 μm. From this acid, using the diphenyl ether procedure, was obtained a 24% yield of **5c:** mp 187–188 °C (benzene/hexane); mixture melting point with the product obtained from **4c,** 187–189 °C; IR 5.87, 6.14 (sh), 6.25 μm. The ^1H NMR data (Tables II and III) also indicate that these compounds are identical.

2-Oxopyrimido[2,1-*b*]benzothiazole (6a). A mixture of the ester **3a** (5.00 g, 19.2 mmol) in 200 mL of 1% NaOH solution was refluxed for 20 min. The solution was cooled and poured into 50 mL of 10% HCl, and the mixture was boiled for 15 min. The solid was collected by filtration, washed with water, and dried to give 4.53 g (96%) of 2-oxopyrimido[2,1-*b*]benzothiazole-4-carboxylic acid: mp 197–198 °C dec; IR 5.85, 6.01, 6.20, 6.38 μm.

The acid (1.35 g, 5.48 mmol), in 30 mL of diphenyl ether, was heated to 250 °C and then allowed to cool to precipitate a solid. The mixture was diluted with ether, and the solid was collected by filtration and recrystallized (charcoaled) from DMF to yield 0.51 g (46%) of **6a:** mp 277–278 °C (lit.[1] mp 272–275 °C); IR 6.10, 6.13 (sh), 6.22 (sh), 6.32 μm.

Anal. Calcd for $C_{10}H_6N_2OS$: C, 59.4; H, 3.0; N, 13.9. Found: C, 59.1; H, 2.9; N, 13.9.

2-Oxopyrimido[2,1-*b*]benzoxazole (6b). A mixture of the ester **3b** (13.0 g, 53.2 mmol) and NaOH (2.4 g, 60 mmol) in 250 mL of water was warmed at 70 °C for 1 h, during which time all of the solids dissolved. The solution was acidified with concentrated HCl (5 mL) to precipitate a solid which was collected by filtration, washed with water, and dried to give 7.28 g (60%) of 2-oxopyrimido[2,1-*b*]benzoxazole-4-carboxylic acid: mp 347–349 °C dec; IR 5.80, 6.02, 6.10, 6.20 μm.

This acid (4.00 g, 17.4 mmol), in 50 mL of diphenyl ether, was refluxed for 30 min, and the solution was allowed to cool and diluted with 300 mL of hexane. The resulting solid was collected by filtration and recrystallized (charcoaled) from ethanol to give 2.77 g (86%) of **6b:** mp 250–252 °C; IR 5.93, 6.00 (sh), 6.04, 6.12 μm.

Anal. Calcd for $C_{10}H_6N_2O_2$: C, 64.6; H, 3.3; N, 15.1. Found: C, 64.2; H, 3.2; N, 15.1.

10-Methyl-2-oxopyrimido[2,1-*b*]benzimidazole (6c). Use of the above base hydrolysis procedure was applied with ester **3c** to give a 78% yield of 10-methyl-2-oxopyrimido[2,1-*b*]benzimidazole-4-carboxylic acid: mp 247–248 °C dec; IR 5.76, 6.05 μm.

A mixture of this acid (3.16 g, 13.0 mmol) and ~0.5 g of copper powder in 25 mL of quinoline was heated up to 170 °C, filtered while hot to remove the copper powder, and then allowed to cool to room temperature. The mixture was diluted with ether to precipitate a solid which was collected by filtration, washed with ether, and recrystallized (charcoaled) from ethanol to give 1.40 g (54%) of **6c:** mp 257–258 °C; IR 6.00, 6.11, 6.20 μm.

Anal. Calcd for $C_{11}H_9N_3O$: C, 66.3; H, 4.6; N, 21.1. Found: C, 65.8; H, 4.9; N, 21.3.

2-(2-Carbethoxy-2-carboxyethyleneimino)benzoxazole (8). A mixture of the ester **4b** (11.0 g, 42.7 mmol) and NaOH (1.9 g, 48 mmol) in 350 mL of water was warmed at ~50 °C until solution was complete (~90 min). The solution was acidified with concentrated HCl (5 mL) and cooled to precipitate a solid which was collected by filtration, washed with water, and dried to give 8.09 g (69%) of **8:** mp 241–242.5 °C; IR 5.70, 5.85, 6.00, 6.13, 6.22 μm; ^1H NMR δ 8.20 (s, 1), 7.4–6.7 (m, 4), 4.17 (q, 2, J = 7 Hz), 1.23 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.5; H, 4.4; N, 10.1. Found: C, 56.0; H, 4.4; N, 10.2.

Methyl 4-Oxopyrimido[2,1-*b*]benzoxazole-3-carboxylate (9). A mixture of 2-aminobenzoxazole (28.6 g, 0.152 mol) and dimethyl ethoxymethylenemalonate[7] (20 g, 0.15 mol) in 300 mL of ethanol was refluxed for 28 h and then cooled to precipitate a solid which was collected by filtration to give 18.8 g (45%) of the intermediate diester 2-[2,2-bis(carbomethoxy)ethyleneimino]benzoxazole: mp 118–120 °C; IR 5.75, 6.00, 6.10, 6.20, 6.31 μm; ^1H NMR ($CDCl_3$) δ 11.2 (s, 1), 8.72 (s, 1), 7.7–7.2 (m, 4), 3.87 (s, 3), 3.80 (s, 3).

This diester (18.8 g, 68.1 mmol), in 200 mL of Dowtherm A, was refluxed under a Dean-Stark trap for 4 h, collecting the methanol as it boiled out of the reaction vessel. The mixture was allowed to cool and diluted with 750 mL of hexane to precipitate a solid which was collected by filtration to yield 15.0 g (90%) of **9:** mp 165–167 °C (ethanol); IR 5.80 μm; ^1H NMR ($CDCl_3$) δ 8.73 (s, 1), 8.39 (m, 1), 7.6–7.2 (m, 3), 3.97 (s, 3).

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Registry No.—2a, 58099-49-3; **2b,** 69461-78-5; **2c,** 69461-79-6; **3a,** 50290-39-6; **3b,** 50290-41-0; **3c,** 69461-75-2; **4a,** 21786-89-0; **4a** intermediate diester, 21418-25-7; **4b,** 40519-89-9; **4b** intermediate diester,

21418-41-7; **4c**, 50532-93-9; **5a**, 32278-63-0; **5b**, 69461-76-3; **5c**, 50532-97-3; **6a**, 32278-445-8; **6b**, 50290-40-9; **6c**, 50532-91-7; **8**, 69461-77-4; **9**, 69461-80-9; **10**, 69461-81-0; DMAF, 7542-94-1; DMAD, 762-42-5; DEEM, 87-13-8; dimethyl ethoxymethylenemalonate, 24362-46-7; 2-aminobenzothiazole, 136-95-8; 2-amino-1-methylbenzimidazole, 1622-57-7; 2-aminobenzoxazole, 4570-41-6; 4-oxopyrimido[2,1-*b*]benzothiazole-3-carboxylic acid, 21786-97-0; 4-oxopyrimido[2,1-*b*]benzothiazole-2-carboxylic acid, 69461-82-1; 4-oxopyrimido[2,1-*b*]benzoxazole-3-carboxylic acid, 69461-83-2; 4-oxopyrimido[2,1-*b*]benzoxazole-2-carboxylic acid, 69461-84-3; 10-methyl-4-oxopyrimido[2,1-*b*]benzimidazole-3-carboxylic acid, 50532-94-0; 10-methyl-4-oxopyrimido[2,1-*b*]benzimidazole-2-carboxylic acid, 69461-85-4; 2-oxopyrimido[2,1-*b*]benzothiazole-4-carboxylic acid, 58099-50-6; 2-oxopyrimido[2,1-*b*]benzoxazole-4-carboxylic acid, 69461-86-5; 10-methyl-2-oxopyrimido[2,1-*b*]benzimidazole-4-carboxylic acid, 69461-87-6; 2-[2,2-bis(carbomethoxy)-ethyleneimino]benzoxazole, 69461-88-7.

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Reaction of 2*H*-Benzimidazole-2-thione with Dimethyl Acetylenedicarboxylate

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The reaction of dimethyl acetylenedicarboxylate (DMAD) with 2*H*-benzimidazole-2-thione in methanol has been investigated. When run for prolonged reaction times, the exclusive product of this reaction, in high yield, is methyl 4-oxo-4*H*-[1,3]thiazino[3,2-*a*]benzimidazole-2-carboxylate. This is also the exclusive product after short reaction times in the presence of a catalytic amount of sodium methoxide. The structure of the product was confirmed by its hydrolysis and decarboxylation to the same product obtained from the reaction of ethyl propiolate with 2*H*-benzimidazole-2-thione. When reactions with DMAD are run for shorter periods of time in methanol, without added base, mixtures of three products can be obtained. Each of these compounds was isolated and characterized. One of them, 2-(carbomethoxymethylene)-3-oxo-2*H*,3*H*-thiazolo[3,2-*a*]benzimidazole, rearranges in methanol to the isomeric thiazinone, and this rearrangement can be catalyzed by methanolic sodium methoxide.

In the course of a medicinal chemical project in our laboratories, I became interested in the reaction of dimethyl acetylenedicarboxylate (DMAD) with 2*H*-benzimidazole-2-thione. A recent report by McKillop et al.[1] prompts this report since my results differ significantly from those which they have described.

An earlier report by Grinblat and Postovskii indicated that the reaction of DMAD with 2*H*-benzimidazole-2-thione (**1**) in glacial acetic acid yields the thiazolidinone **3**, mp 190–192 °C.[2] Theoretically, several other products of such a reaction are possible, perhaps the most notable possibility being the thiazinone **4**, which might be formed from the presumed intermediate Michael adduct **2** by reaction of the ring nitrogen with the other ester functionality (see Scheme I). It seemed possible that the Russian workers might have actually isolated **4** instead of **3**. The relevant literature, although somewhat confusing, seems to bear out their structural assignment, however. Thus, the reaction of DMAD with N,N′-disubsti-

Scheme I