Synthesis and *X*-Ray Structure of Methyl 2-Oxopyrimido[2,1-*b*]benzothiazole-4-carboxylate from Condensation of 2-Aminobenzothiazole and Dimethyl But-2-ynedioate

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The product from 2-aminobenzothiazole and dimethyl but-2-ynedioate has been shown by *X*-ray analysis to be the title compound (IIIa). Crystals of (IIIa) are monoclinic, space group $P2_1/c$, with a = 4.801(5), b = 13.68(1), c = 20.37(2) Å, β = 90.44(5)°, and Z = 4. The structure was solved by direct methods and refined by full-matrix least-squares to R 0.099 for 1 931 observed photographic intensities.

The molecule consists of an exocyclic carbonyl group and a methyl ester group linked to a slightly warped C_6–C_3NS–C_4N_2 ring skeleton. The carboxy-group makes a dihedral angle of 34° with the mean plane of the heterocyclic ring system. The sulphur atom participates in the molecular π-bonding, and bond-length variations in the tricyclic ring system are well accounted for in terms of simple Hückel MO theory.

A reaction mechanism is suggested which involves an initial Michael addition on an acetylenic carbon by the ring nitrogen, forming an enamine with the fumarate structure. Subsequent ring-closure involving the β-methoxycarbonyl- and imino-groups leads to the formation of the product.

THE utility of dimethyl but-2-ynedioate (I) in the synthesis of heterocyclic compounds is well established. When (I) reacts with amines, the primary product is, depending on solvent polarity, an enamine with the maleate or fumarate structure.[1] For aromatic amines and compounds containing more than one nitrogen atom, the enamine may undergo thermal cyclization to give heterocyclic compounds.[2] When (I) reacts with a compound containing sulphur as the donor atom, the product is usually a thioheterocyclic compound.[3]

The existence of tautomeric forms (IIa) and (IIb) [4] in 2-aminobenzothiazole (II) provides a unique situation in which both nitrogen atoms* can act as nucleophiles. Thus, in an effort to gain further insight into the reaction of (I) with nitrogen- and sulphur-containing heterocycles, the condensation of (I) and (II) was examined. For the single product obtained from this reaction, the measured i.r., u.v., n.m.r., and mass spectral data did not provide a unique distinction between suggested structures (IIIa) and (IIIb). An attempt was therefore made to establish the structure unequivocally by *X*-ray analysis.

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[3] L. W. Lown and J. C. N. Ma, *Canad. J. Chem.*, 1967, **45**, 939, 953; N. D. Heindel, V. B. Fish, M. F. Ryan, and A. R. Lepley, *J. Org. Chem.*, 1967, **32**, 2678; D. L. Coffen, *Tetrahedron Letters*, 1970, 2633; H. Nagase, *Chem. and Pharm. Bull.* (*Japan*), 1973, **21**, 279.

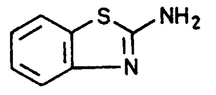
[4] K. Nagarajan and V. R. Rao, *Indian J. Chem.*, 1969, **7**, 964.

EXPERIMENTAL

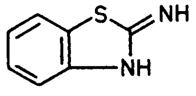
Preparation of (III).—Several recrystallizations of a commercial sample of (II) yielded silvery white plate-shaped crystals, m.p. 124—125 °C. Compound (I) (2.3 g, 16.2 mmol, excess) was added dropwise to a solution of (II) (2.3 g, 15.3 mmol) in methanol (40 ml). After the reaction mixture had been set aside in the dark under nitrogen for several days, there was a massive crop of crystals of stoicheiometry $C_{12}H_8N_2O_3S$ (92%) m.p. 183—185 °C; i.r.: $\bar{\nu}$ 1 725 (ester C=O), 1 650 (amide C=O), 1 365 (methylene C–H), 1 280 (aromatic amine C–N), 1 240 (ester C–O), 730—770 (aromatic C–H) cm^{-1}; u.v.: $\lambda_{max.}$ 374 nm; n.m.r. ($CDCl_3$): δ 4.02 (s, 3 H), 6.05 (s, 1 H), 7.35 (m, 4 H); mass spectrum (70 eV): *m/e* 232 (relative abundance 24), 201 (79), 176 (21), 174 (14), 146 (34%).

$MeO_2C{\cdot}C{:}C{\cdot}CO_2Me$

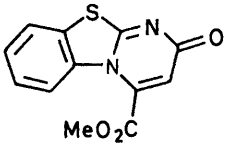
(I)



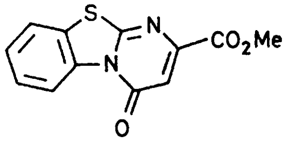
(IIa)



(IIb)



(IIIa)



(IIIb)

Crystal Data.—$C_{12}H_8N_2O_3S$, $M = 260.28$. Monoclinic, $a = 4.801(5)$, $b = 13.68(1)$, $c = 20.37(2)$ Å, $\beta = 90.44(5)$°, $U = 1\,134$ Å^3, $D_m = 1.518(5)$ (by flotation), $Z = 4$, $D_c = 1.524$ g cm^{-3}, $F(000) = 536$. Space group $P2_1/c$ (No. 14) from systematic absences ($h0l$, l odd; $0k0$, k odd) and intensity statistics. Cu-K_α radiation, $\lambda = 1.541\,8$ Å; μ(Cu-K_α) = 25.0 cm^{-1}.

Crystallographic Measurements.—Single crystals for *X*-ray analysis were selected from samples grown in a dilute solution of the compound in methanol. Crystals were yellow needles elongated along *a* and well-developed on the (012) face. Unit-cell dimensions were determined from high-angle reflections on $0kl$ and $h0l$ Weissenberg photographs.

For the collection of intensity data a crystal of dimensions 0.7 (needle axis) × 0.16 × 0.19 mm was mounted along the *a* axis. Another crystal of dimensions 0.37 × 0.24 × 0.43 mm (needle axis) was initially mounted along a face diagonal of the cross-section perpendicular to the needle axis, and was subsequently oriented to rotate about the *b* axis. The 0—$3kl$ and $h0$—$13l$ levels were recorded on Weissenberg photographs by use of nickel-filtered Cu-K_α radiation, and the multiple-film technique was used to correlate strong and weak reflections. Intensities were estimated visually by comparison with a calibrated strip Data were corrected as usual for Lorentz and polarization factors, but not for absorption or extinction. Finally a set of scaled structure amplitudes was derived by correlating equivalent reflections with a least-squares procedure.[5] After reduction data consisted of 1 931 independent reflections of measurable intensity and 593 unobserved reflections.

Structure Determination.—The structure was solved by direct phase-determination using the multi-solution program MULTAN.[6] The calculation was performed with 328 normalized structure factors of values >1.5. The set of phases with the highest figure of merit (1.186) was used in computing an *E* map which revealed the positions of all eighteen non-hydrogen atoms in the molecule (Figure 1). The structure was refined by full-matrix least-squares; owing to limitation in the available core, only atoms S, O(1), O(2), O(3), C(11), and C(12) were varied anisotropically; *R* for the 1 931 observed reflections was then 0.110. Further refinement was attempted by the introduction of ring hydrogen atoms. Instead of locating the hydrogen atomic co-ordinates from a difference map, they were ' generated ' using a computer program based on an algorithm similar to that given for the X_3CH group by Rollett.[7] Inclusion of five hydrogen atoms with the same isotropic temperature factor (B 6.0 Å^2) in a last cycle of refinement yielded a final *R* of 0.099. The parameter shifts were small compared to the respective standard deviations.

Computation was carried out on an ICL 1904A with a local adaptation of the program LALS.[8] The function minimized was $\Sigma w(|F_o| - |F_c|)^2$, the weighting scheme used being that of Cruickshank *et al.*[9] with $w = (2F_{min.} + |F_o| + 2|F_o|^2/F_{max.})^{-1}$, where $F_{min.}$ and $F_{max.}$ were taken as 1.0 and 145.0 respectively. *X*-Ray scattering factors were taken from ref. 10.

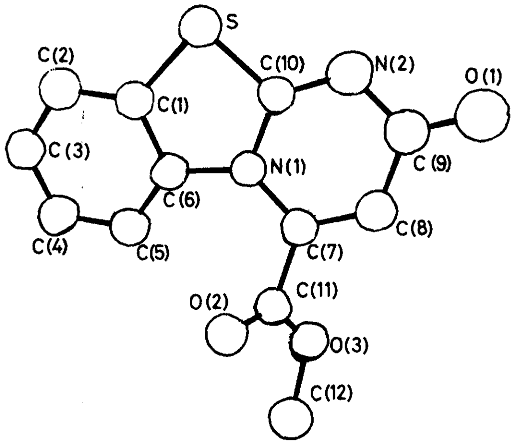


FIGURE 1 Perspective drawing of the molecule showing the labelling of the atoms

RESULTS

Final positional and thermal parameters of the atoms are listed in Table 1. Table 2 contains the interatomic distances and angles, the estimated standard deviations of which include contributions from the variance–covariance matrix and errors in unit-cell dimensions. Figure 1 shows the

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[5] W. C. Hamilton, J. S. Rollett, and R. A. Sparks, *Acta Cryst.*, 1965, **18**, 129.

[6] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.

[7] ' Computing Methods in Crystallography,' ed. J. S. Rollett, Pergamon Press, London, 1965, p. 31.

[8] ' World List of Crystallographic Computer Programs,' 2nd edn., ed. D. P. Shoemaker, Internat. Union Crystallography, 1966, Program Accession No. 384.

[9] ' Computing Methods and the Phase Problem in *X*-Ray Crystal Analysis,' eds. R. Pepinsky, J. M. Robertson, and J. C. Speakman, Pergamon Press, Oxford, 1961, p. 45.

[10] ' International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962, pp. 202—207.

molecule and indicates the labelling scheme. Observed and calculated structure factors and results of MO calculations are deposited as Supplementary Publication No. 21979 (15 pp., 1 microfiche).*

DISCUSSION

The present analysis has shown that compound (III) has the structure (IIIa) (methyl 2-oxopyrimido[2,1-*b*]benzothiazole-4-carboxylate).[11]

The equation to the mean plane of the 2-oxopyrimido[2,1-*b*]benzothiazole molecular skeleton is $0.8654X - 0.3507Y - 0.3578Z = -1.4032$ (where X, Y, and Z are orthogonal Å co-ordinates referred to axes directed along a, b, and c^*). The deviations of individual atoms from this plane (last column of Table 1) clearly show that the molecular skeleton is significantly warped. The normal to the ring system is inclined by 30.1° to the a axis. The planar carboxy-group tilts towards the ring skeleton by 34° from its idealized perpendicular orientation (Figure 1).

TABLE 1

Atomic fractional co-ordinates ($\times 10^4$) and thermal parameters ($\times 10^4$ Å^2), with estimated standard deviations in parentheses. Deviations ($\times 10^4$ Å) of relevant atoms from their mean plane are given in the last column

Atoms	x	y	z	U	δ
S	3 548(4)	1 782(1)	2 384(1)	*	32
O(1)	5 928(12)	5 101(3)	1 572(2)	*	−117
O(2)	2 946(10)	2 100(3)	−0 211(2)	*	
O(3)	−0 461(10)	3 383(3)	−0 298(2)	*	
N(1)	2 129(9)	2 438(3)	1 221(2)	533(9)	79
N(2)	4 904(11)	3 557(4)	1 943(2)	690(11)	−13
C(1)	1 402(13)	1 017(4)	1 840(3)	600(11)	45
C(2)	0 285(14)	0 077(4)	1 971(3)	715(14)	3
C(3)	−1 505(14)	−0 389(5)	1 490(3)	721(14)	−48
C(4)	−2 213(14)	0 074(4)	0 900(3)	696(14)	−82
C(5)	−1 160(13)	1 007(4)	0 769(3)	628(13)	−61
C(6)	0 735(12)	1 476(4)	1 235(2)	547(11)	38
C(7)	2 147(12)	3 115(4)	0 719(2)	570(11)	133
C(8)	3 282(14)	4 022(4)	0 833(3)	687(14)	15
C(9)	4 784(15)	4 283(4)	1 470(3)	702(14)	−53
C(10)	3 601(12)	2 718(4)	1 808(2)	589(11)	29
C(11)	1 569(13)	2 781(4)	0 019(2)	*	
C(12)	−0 924(17)	3 164(5)	−1 001(3)	*	
H(1)	0 880	−0 245	2 365		
H(2)	−2 108	−1 088	1 571		
H(3)	−3 238	−0 220	0 542		
H(4)	−1 753	1 348	0 335		
H(5)	3 049	4 571	0 454		

* Anisotropic thermal parameters of the form

$$\exp[-2\pi^2 \sum_i \sum_j U_{ij} h_i h_j a_i^* a_j^*]$$

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S	670(9)	838(10)	438(6)	37(6)	−9(5)	30(6)
O(1)	1 193(38)	691(27)	897(33)	−132(25)	−159(27)	−89(24)
O(2)	867(27)	742(24)	517(20)	96(20)	55(18)	−65(18)
O(3)	744(24)	798(27)	491(19)	70(19)	−28(17)	46(18)
C(11)	634(29)	670(29)	490(25)	−37(24)	59(21)	28(23)
C(12)	895(42)	1 068(47)	469(27)	18(27)	−22(27)	61(28)

The two C–S bonds in the thiazole ring have values intermediate between those for a single (1.808) and a double bond (1.556 Å),[12] but are longer than the value of C–S (1.714 Å) in thiophene.[12] The length (1.753 Å) for C(1)–S compares well with that (1.759 Å) in 1,4-bis-(*N*-ethyl-1,2-dihydrobenzothiazol-2-ylidene)tetrazene.[13] The C(10)–S bond (1.737 Å) is also in good agreement with the value (1.733 Å) for 1,2,3,8a-tetrahydro-3-phenyl-2-phenyliminothiazolo[3,2-*a*]-*s*-triazine-4-thione.[14] The C–S–C bond angle (91°) agrees well with values determined for other benzothiazole systems.[15] Obviously the *p* orbitals of the sulphur atom play an important role in the bonding scheme.

TABLE 2

Bond lengths (Å) and bond angles (°), with estimated standard deviations in parentheses. HMO π-bond orders ($\times 10^3$) are given in square brackets

(*a*) Distances

S–C(1)	1.753 (5) [315]	N(2)–C(10)	1.294 (7) [630]
S–C(10)	1.737 (6) [440]	C(1)–C(2)	1.391 (8) [632]
O(1)–C(9)	1.230 (8)	C(1)–C(6)	1.408 (8) [610]
O(2)–C(11)	1.187 (7)	C(2)–C(3)	1.375 (9) [679]
O(3)–C(11)	1.332(7)	C(3)–C(4)	1.388 (9) [651]
O(3)–C(12)	1.474 (7)	C(4)–C(5)	1.373 (8) [679]
N(1)–C(6)	1.434 (6) [308]	C(5)–C(6)	1.377 (7) [634]
N(1)–C(7)	1.380(6) [411]	C(7)–C(8)	1.344 (8) [819]
N(1)–C(10)	1.387 (7) [466]	C(8)–C(9)	1.475 (9) [488]
N(2)–C(9)	1.384 (8) [606]		

(*b*) Angles

C(1)–S–C(10)	91.2(3)	N(1)–C(6)–C(5)	129.4(5)
C(11)–O(3)–C(12)	114.9(5)	C(1)–C(6)–C(5)	119.9(5)
C(6)–N(1)–C(7)	129.4(4)	C(11)–C(7)–N(1)	119.6(4)
C(6)–N(1)–C(10)	113.9(4)	C(11)–C(7)–C(8)	119.5(5)
C(7)–N(1)–C(10)	116.6(4)	N(1)–C(7)–C(8)	119.7(5)
C(9)–N(2)–C(10)	118.5(5)	C(7)–C(8)–C(9)	121.0(5)
S–C(1)–C(2)	126.3(4)	O(1)–C(9)–N(2)	121.6(6)
S–C(1)–C(6)	112.3(4)	O(1)–C(9)–C(8)	121.6(6)
C(2)–C(1)–C(6)	121.3(5)	N(2)–C(9)–C(8)	116.8(5)
C(1)–C(2)–C(3)	117.7(6)	S–C(10)–N(1)	111.8(4)
C(2)–C(3)–C(4)	120.8(6)	S–C(10)–N(2)	121.2(4)
C(3)–C(4)–C(5)	121.9(5)	N(1)–C(10)–N(2)	127.1(5)
C(4)–C(5)–C(6)	118.3(5)	O(2)–C(11)–O(3)	126.0(5)
N(1)–C(6)–C(1)	110.6(4)	O(2)–C(11)–C(7)	122.6(5)
		O(3)–C(11)–C(7)	111.3(4)

The C(6)–N(1) bond length (1.434 Å) is shorter than the mean C–N single-bond distance (1.47 Å),[16] but longer than corresponding bonds in benzothiazoles.[15] Being the bridge between two six-membered rings, the C(6)–N(1) bond suffers most severely from angular strain caused by formation of the central C$_3$NS ring; the net effect is a significant lengthening of this bond. In contrast, the C(10)–N(2) bond in the C$_4$N$_2$ ring has a value (1.294 Å) characteristic of C–N double bonds.[16] Other C–N

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* For details, see Notice to Authors No. 7, in *J.C.S. Perkin II*, 1975, Index issue.

[11] 'The Ring Index,' 2nd edn., eds. A. M. Patterson, L. T. Capell, and D. F. Walker, Amer. Chem. Soc., 1960, p. 348.

[12] B. Bak, D. Christensen, L. Hansen-Nygaard, and J. Rastrap-Anderson, *J. Mol. Spectroscopy*, 1961, **7**, 58.

[13] R. Allmann, *Acta Cryst.*, 1967, **22**, 246.

[14] J. Karle, J. Flippen, and I. L. Karle, *Z. Krist.*, 1967, **125**, pp. 115, 210.

[15] P. J. Wheatley, in 'Physical Methods in Heterocyclic Chemistry,' vol. V, ed. A. R. Katritzky, Academic Press, New York, 1972, p. 321.

[16] B. Bak and L. Hansen-Nygaard, *J. Chem. Phys.*, 1960, **33**, 418.

bond distances in the molecule have values close to 1.38 Å, intermediate between single and double C–N bonds and therefore indicative of a high degree of π-bonding. The short C(10)–N(2) and C(7)–C(8) bonds, together with the pattern of bond-length and -angle variations in the C_4N_2 ring, reflect the ' quinonoid ' character imposed on this ring by the exocyclic C=O bond and the bridging nitrogen atom as suggested by the valence-bond structural formula (IIIa).

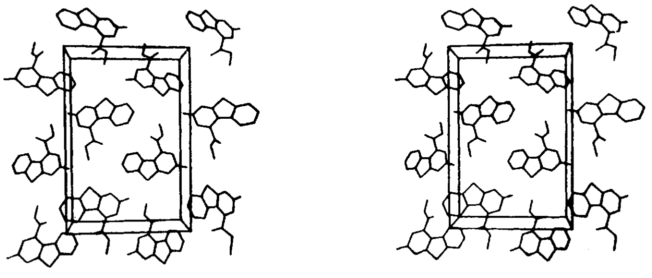
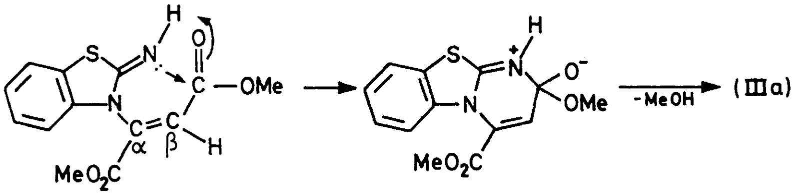


FIGURE 2 Stereodrawing showing the packing of the molecules viewed along the *a* axis towards the origin

The dimensions of the benzene ring are as expected, as are those of the exocyclic C=O and methyl ester groups.



(V)

SCHEME

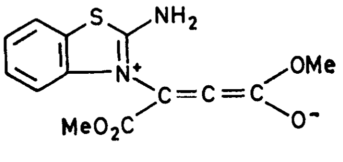
However, the C(7)–C(11) bond of (1.514 Å) approaches the natural sp^2–sp^2 bond length as suggested by Mulliken,[17] and provides additional evidence for the lack of conjugation of the ester group with the main skeleton of the molecule.

Figure 2 shows the mode of molecular packing viewed along *a*. All intermolecular contacts correspond to normal van der Waals separations. Stacking of the molecules in piles along *a*, and also in dense layers approximately parallel to (012), provides a rationale for the crystal morphology.

Bonding Model.—As the molecular skeleton of (IIIa) is essentially planar, the π electrons are expected to be extensively delocalized. The S atom, with a C–S–C bond angle of *ca.* 90°, resembles the sulphur atom in thiophen. Similarly, the N(1) atom resembles the nitrogen atom in pyrroles. Both atoms will contribute the electron pairs in their p_z orbitals to the molecular π-bonding.

Huckel molecular orbitals (HMO) for the molecular skeleton were calculated by use of a Fortran IV program.[18] Parameters for the heteroatoms were assigned according to the empirical rules of Streitwieser:[19] for S, h 1.5, k 0.8; for N(1), h 1.5, k 0.8; for N(2), h 0.5, k 1.0; for O(1), h 1.0, k 1.0. The results are given in the Supplementary Publication.

The lengths of the C–C bonds can be correlated fairly well with the π-bond orders as can be seen from Table 2. As a quantitative test of the validity of the HMO model, C–C bond lengths r were calculated from the equation [20] $r = s - (s - d)/[1 + k(1 - p)/p]$, where $s = 1.515$ Å is a pure sp^2–sp^2 carbon bond length, $d = 1.335$ Å a double bond length, p the π-bond order, and k a constant equal to 1.05.[21] The agreement between calculated and measured values, though far from ideal, is satisfactory considering the crudeness of the model. In particular, the trend of variation is well reproduced. The bond length–bond order correlation (Table 2) also holds well for the C–S and C–N bonds.



(IV)

The u.v. absorption band at 374 nm can be explained as the electronic transition from the highest-occupied orbital to the lowest-vacant orbital, with an energy difference of 1.304 β. Taking β as 55 kcal mol^{-1},[22] this energy difference corresponds to a transition wavelength of 398 nm, which is in reasonable agreement with the experimental value.

Reaction Mechanism.—Judging from the structure of the product, the reaction between (I) and (II) most likely involves an initial Michael addition of the ring nitrogen to the acetylenic function, giving rise to the allene intermediate (IV) which would be stabilized by resonance. Previous reports on the reaction of (I) with amines[1] indicate that *trans*-addition is favoured in a polar solvent medium, as in the present case. The ring skeleton then loses a proton through the amino-nitrogen to give the enamine with fumarate structure (V).

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[17] R. S. Mulliken, *Tetrahedron*, 1959, **6**, 68.

[18] H. H. Greenwood, ' Computing Methods in Quantum Organic Chemistry,' Wiley, New York, 1972.

[19] A. Streitwieser, ' Molecular Orbital Theory for Organic Chemists,' Wiley, New York, 1961, ch. 5.

[20] C. A. Coulson, *J. Phys. Chem.*, 1952, **56**, 311.

[21] Ref. 19, p. 167.

[22] Ref. 19, p. 176.

Further reaction is possible between the α- or β-ester and the exocyclic sp^2-hybridized nitrogen. The carbonyl carbons are required to be in the proximity of the exocyclic (imino) nitrogen to facilitate ring closure. With the use of a Dreiding stereomodel, it can be readily demonstrated that the carbonyl carbon of the α-ester can never be as close to the nitrogen atom as its counterpart in the β-ester; furthermore, when the former is brought into a position favouring reaction with the imino-nitrogen by rotation about the C–N single bond, serious crowding between the benzene ring and the β-ester group results. Cyclization therefore proceeds *via* the pathway shown in the Scheme.

Unlike the reaction of thiourea with (I), the sulphur atom in (II) does not participate in the addition. This is to be expected, since the sulphur atom has lost its basicity by contributing an electron pair to the molecular π-bonding.

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