

THE MOLECULAR STRUCTURE OF  
7-DEMETHOXY-7-*p*-BROMOANILINO  
MITOMYCIN B

Sir:

In 1956, HATA *et al.* isolated the mitomycin, a series of anticancer antibiotics shown in Table 1, from the fermentation beer of *Streptomyces caesipitosus*.<sup>1)</sup> Mitomycin C is now widely used in cancer chemotherapy.

Mitomycin C and profiromycin can be obtained from mitomycin A by chemical reactions, but mitomycin B was not derived directly from, or converted to any of the other three antibiotics.

The absolute structure of mitomycin A was confirmed by X-ray analysis of N-brosylmitomycin A (I) by TULINSKY in 1965 as shown in Fig. 1.<sup>2)</sup>

In this communication, we describe the result of X-ray structure determination of mitomycin B. A heavy atom derivative, 7-demethoxy-7-*p*-bromoanilino mitomycin B (II), was synthesized from mitomycin B and *p*-bromoaniline stirred in methanol for 18 hours at 50°C. Single crystals were grown from an acetone solution by slow evaporation in a chamber saturated with aqueous vapor. Crystal data are as follows: C<sub>21</sub>H<sub>21</sub>N<sub>4</sub>O<sub>5</sub>Br·H<sub>2</sub>O, MW

Fig. 1. Absolute configuration of mitomycin A

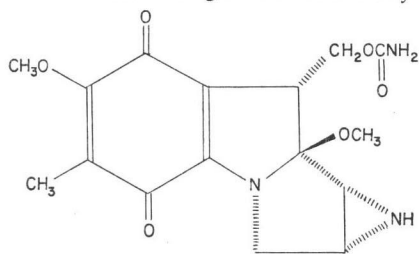


Fig. 2. Absolute molecular structure of 7-demethoxy-7-*p*-bromoanilino mitomycin B

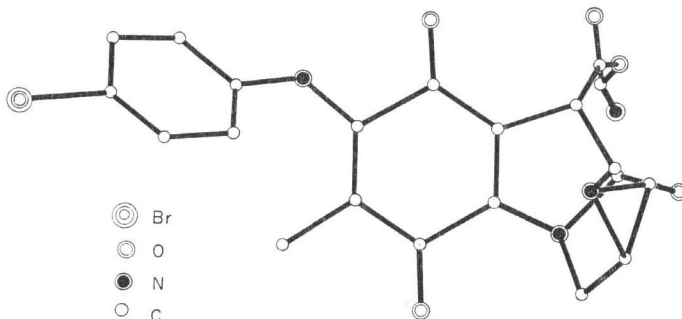
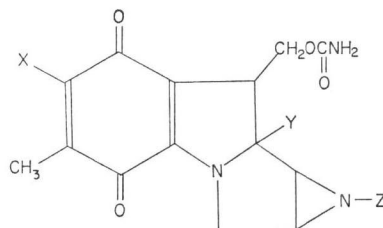


Table 1.



Compound	X	Y	Z
Mitomycin A	OCH <sub>3</sub>	OCH <sub>3</sub>	H
Mitomycin B	OCH <sub>3</sub>	OH	CH <sub>3</sub>
Mitomycin C	NH <sub>2</sub>	OCH <sub>3</sub>	H
Profiromycin	NH <sub>2</sub>	OCH <sub>3</sub>	CH <sub>3</sub>

=507.39, Orthorhombic,  $p2_12_12_1$ ,  $a=29.195 \pm 0.009$ ,  $b=9.245 \pm 0.005$ ,  $c=7.940 \pm 0.005 \text{ \AA}$ ,  $Z=4$ ,  $D_x=1.56$ ,  $D_m=1.57 \text{ g cm}^{-3}$ ,  $\mu(\text{Cu-K}\alpha)=31.71 \text{ cm}^{-1}$ . Intensity data were collected using Ni-filtered Cu-K $\alpha$  radiation on equi-inclination multiple-film WEISSENBERG photographs.

The intensity data were measured by visual comparison with a standard scale. 2385 independent reflections were collected; 495 of them were regarded as zero.

LORENTZ and polarization corrections were made as usual, but the absorption correction was omitted. The dimensions of the crystals used were  $0.04 \times 0.5 \times 0.3 \text{ mm}$ .

The structure was solved by the heavy atom method and refined by the block-diagonal least-squares method allowing anisotropic temperature factors for each atom. The final R value was 0.119 for 1890 observed reflections. The absolute configuration was established using anomalous dispersion of the bromine atom ( $\Delta f' = -0.9$ ,  $\Delta f'' = 1.5$ ) for Cu-

Table 2. Final atomic parameters

All quantities are multiplied by  $10^4$ . E.s.d.'s are in parentheses. The anisotropic temperature factors are of the form  $T = \exp -(\text{B}_{11}h^2 + \text{B}_{22}k^2 + \text{B}_{33}l^2 + \text{B}_{12}hk + \text{B}_{13}hl + \text{B}_{23}kl)$ . O 32 is attributed to the water of crystallization. To represent the correct absolute configuration, the  $x, y, z$  coordinates should be referred to the right hand coordinate system.

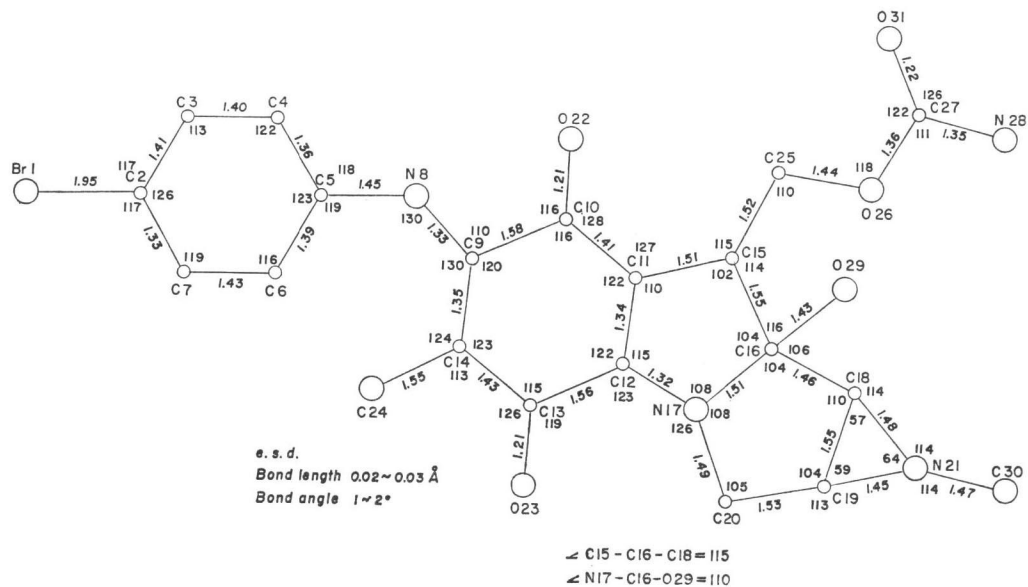
	$x/a$	$y/b$	$z/c$	$\text{B}_{11}$	$\text{B}_{22}$	$\text{B}_{33}$	$\text{B}_{12}$	$\text{B}_{13}$	$\text{B}_{23}$
Br 1	0902(1)	10906(3)	1222(4)	9(0)	332(5)	494(7)	41(2)	0(2)	-253(11)
C 2	1534(4)	10355(20)	0778(26)	7(1)	233(33)	318(46)	64(12)	-15(14)	-253(69)
C 3	1813(5)	11395(22)	-0017(24)	11(2)	226(34)	238(39)	48(14)	-4(15)	-41(69)
C 4	2258(5)	10911(18)	-0323(25)	11(1)	119(21)	321(46)	43(11)	-2(15)	-55(59)
C 5	2401(4)	9576(16)	0152(22)	6(1)	115(20)	263(36)	10(8)	-11(12)	-25(50)
C 6	2127(4)	8620(17)	1044(22)	8(1)	143(23)	210(33)	-9(9)	-5(13)	-82(53)
C 7	1665(4)	9061(19)	1321(22)	8(1)	164(24)	217(33)	6(11)	-0(13)	-108(60)
N 8	2875(3)	9180(13)	-0170(19)	7(1)	78(14)	337(35)	14(7)	14(11)	45(44)
C 9	3071(4)	7887(14)	-0207(19)	6(1)	82(16)	176(29)	8(8)	9(10)	28(40)
C 10	3581(4)	7999(13)	0440(20)	6(1)	62(15)	213(32)	-12(7)	13(10)	10(37)
C 11	3826(4)	6693(14)	0519(18)	7(1)	73(15)	169(28)	-5(7)	15(10)	-10(37)
C 12	3628(4)	5408(13)	0231(18)	7(1)	57(14)	177(27)	2(7)	11(10)	-31(35)
C 13	3146(4)	5278(15)	-0601(18)	8(1)	100(17)	153(27)	-17(8)	25(10)	-48(39)
C 14	2901(4)	6612(16)	-0740(20)	6(1)	123(19)	189(31)	1(8)	9(11)	19(44)
C 15	4295(3)	6467(12)	1274(20)	4(1)	61(14)	225(30)	3(6)	2(11)	33(39)
C 16	4313(4)	4795(14)	1453(19)	6(1)	107(18)	160(26)	9(8)	10(10)	-91(40)
N 17	3889(3)	4272(11)	0539(14)	7(1)	50(11)	173(22)	-14(6)	4(8)	3(29)
C 18	4257(4)	4250(16)	3164(18)	10(1)	97(18)	167(29)	27(9)	9(10)	30(41)
C 19	3883(5)	3064(15)	3199(20)	12(2)	85(18)	171(32)	-1(10)	19(12)	26(41)
C 20	3737(4)	2901(14)	1364(19)	12(2)	82(16)	131(27)	-1(9)	2(12)	-8(40)
N 21	3796(3)	4501(12)	3872(16)	9(1)	96(15)	157(22)	-11(7)	6(9)	54(35)
O 22	3712(3)	9190(11)	0832(17)	5(1)	86(12)	426(32)	1(6)	-18(9)	-29(39)
O 23	3009(3)	4105(11)	-1035(15)	8(1)	115(13)	265(25)	-16(6)	-2(9)	-100(37)
C 24	2450(5)	6464(20)	-1755(24)	9(2)	200(30)	272(41)	9(12)	-36(14)	-41(63)
C 25	4688(4)	7093(18)	0265(21)	5(1)	153(23)	222(33)	-21(9)	12(11)	-41(49)
O 26	4706(3)	6412(10)	-1369(14)	9(1)	86(12)	197(20)	-12(6)	21(9)	-25(30)
C 27	4976(4)	7036(14)	-2564(24)	6(1)	69(15)	237(30)	-11(8)	7(10)	37(41)
N 28	5013(4)	6189(15)	-3936(17)	13(1)	146(20)	173(26)	-17(9)	23(12)	-63(44)
O 29	4713(2)	4102(10)	0795(14)	5(1)	66(10)	281(24)	14(5)	18(8)	16(30)
C 30	3781(5)	4565(18)	5726(19)	14(2)	145(23)	141(27)	-33(11)	34(12)	-31(46)
O 31	5121(3)	8263(10)	-2415(16)	12(1)	78(12)	232(22)	-14(7)	16(10)	-8(30)
O 32	4557(4)	0339(14)	2136(18)	15(2)	178(21)	328(32)	-27(10)	-2(12)	-13(46)

$K\alpha$  radiation. Comparison of the observed intensities and the calculated structure factors of 24 pairs of  $(hkl)$  and  $(\bar{h}k\bar{l})$  reflections for  $l=1\sim 6$ , indicated the absolute configuration as shown in Fig. 2. The final atomic parameters and their estimated standard deviations are listed in Table 2.

The bond lengths and angles are shown in Fig. 3. C 9-C 10=1.58Å and C 12-C 13=1.56Å are significantly longer than the typical C (SP<sup>2</sup>)-C (SP<sup>2</sup>) single bond length (1.47Å),<sup>3)</sup> and

C 16-C 18=1.46Å is significantly shorter than the typical C (SP<sup>3</sup>)-C (SP<sup>3</sup>) bond length (1.54Å).<sup>3)</sup> It has revealed that the three dimensional structure of **II** is greatly different from that of **I**. The configurations of optical active carbons are C 15 (S), C 16 (R), C 18 (S), and C 19 (S) in (**II**), and C 15 (S), C 16(S), C 18 (R), and C 19 (R) in (**I**). The result of this X-ray analysis is consistent with the fact that mitomycin B has not been derived from or converted to any of the other three mitomycins

Fig. 3. Bond lengths (Å) and bond angles (deg.)



by chemical reactions.

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#### References

1) HATA, T.; Y. SANO, R. SUGAWARA, A.

MATSUMAE, K. KANAMORI, T. SHIMA & T. HOSHI: Mitomycin, a new antibiotic from *Streptomyces*. I. J. Antibiotics, Ser. A 9: 141-146, 1956

2) TULINSKY, A. & J. H. VAN DEN HENDE: The crystal and molecular structure of N-brosyl mitomycin A. J. Amer. Chem. Soc. 89: 2905-2911, 1967

3) SUTTON, L. E.: Tables of interatomic distances and configuration in molecules and ions. Supplement. Special publication No. 18, The Chemical Society, London, 1965