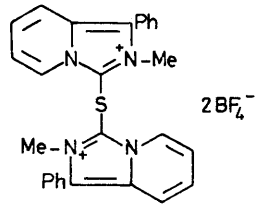
Crystal and Molecular Structure of 3,3′-Thio-bis-(2-methyl-1-phenylimidazo-[1,5-*a*]pyridinium) Bistetrafluoroborate; a Potent New Sulphur-containing Curariform Agent

By DAVID J. POINTER and JOHN B. WILFORD
(*Department of Chemistry, Teesside Polytechnic, Borough Road, Middlesbrough, Cleveland* TS1 3BA)

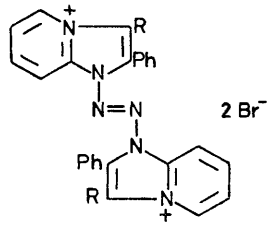
Summary Determination of the *X*-ray structure of the title compound, a new diquaternary monosulphide having potent neuromuscular blocking activity, has shown that the intramolecular distances between potential quaternary nitrogens are less than 4·81 Å; the non-planarity of the molecule is in striking contrast with related compounds which show comparable activity.

RECENTLY proposed[1] molecular criteria for potent competitive neuromuscular blockade include the presence of quaternary nitrogen atoms separated by 10·8(3) Å in a rigid concave molecule which also has suitably disposed oxygen atoms to aid orientation on the receptor site. That these criteria are not critical was first demonstrated by the determination[2,3] of the crystal structure of the near-planar 1,1′-azo-bis-2-phenylimidazo[1,2-*a*]pyridinium dibromide (II) which has a quaternary nitrogen atom separation of 7·5 Å in the crystal.

The title compound (I) has four possible quaternary nitrogen intramolecular separations in the crystal, of which the longest is 4·81 Å, and examination of Dreiding models indicates that there is no conformation in which this separation exceeds 5·0 Å.



(I)



(II) R = H
(III) R = Me

These results clearly reinforce our earlier suggestion[2] that cellular components bearing acetylcholine receptors permit considerable variations of conformation in competitors or alternatively that effective neuromuscular blockade can be accomplished by single-point interaction with a receptor. The tetrazene linkage in the compound (II) and its 3-methyl analogue (III) is believed[4] to be labile in biological systems and may be responsible for their short-acting properties. Other linkages between the imidazopyridine ring systems have been synthesised[4] including mono- and di-sulphides, which are intrinsically unstable in biological systems. The potencies of these postsynaptic non-depolarising agents have been determined in several species[5] and compound (III)† is presently used in clinical practice.[6]

† Compound (III) is now marketed under the name 'Fazadon'.

The monosulphide (I) is suitably active[7] but is not ideal for clinical application because of undesirable side effects.

Crystal data: compound (I), $[C_{28}H_{24}N_4S]^{2+}$ $2BF_4^-$, monoclinic, $a = 15{\cdot}517(2)$, $b = 14{\cdot}054(3)$, $c = 13{\cdot}862(2)$ Å, $\beta = 108{\cdot}88(1)°$, $D_m = 1{\cdot}455$ g cm^{-3}, $D_c = 1{\cdot}445$ g cm^{-3} for $Z = 4$, μ(Cu-K_α) = 17·3 cm^{-1}, space group $P2_1/c$. Equi-inclination Weissenberg photographs with Cu-K_α radiation of c axis layers 0—10 inclusive afforded 1862 visually estimated reflections. The structure was solved by centro-symmetric symbolic addition using the LUX suite of programs[8] with 430 reflections having $|E| > 1{\cdot}35$. Block-diagonal refinement with anisotropic temperature factors for all non-hydrogen atoms in the cation gave a conventional R factor of 0·122. Full-matrix least-squares refinement on data re-estimated by microdensitometry is in progress.

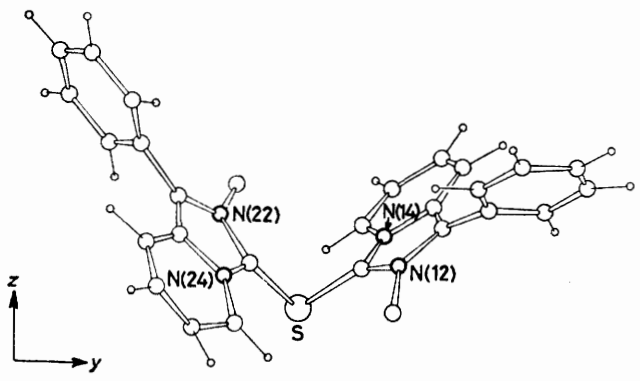


FIGURE. Molecular structure of the title compound (I) viewed along the *a* axis.

The molecular structure is shown in the Figure. Each imidazopyridine ring system is nearly planar and the dihedral angle between their least-squares planes (from which no atom deviates more than 0·04 Å) is 73°. Neither of the phenyl substituents is coplanar with the parent imidazopyridine ring systems and their least-squares planes make angles of 48·5 and 53·5° with those of the parent ring systems to which they are bonded. Non-bonded distances between nitrogen atoms, any of which could be quaternary, are N(12)–N(22), 4·40(2); N(12)–N(24), 4·17(2); N(14)–N(22), 4·02(2), and N(14)–N(24), 4·81(2) Å. The geometry of the sulphur linkage is clearly shown in the Figure, and the C–S bonded distance of 1·70(1) Å and C–S–C bond angle of 103·3(5)° compare well with values recently reported[9] for a sulphur bridge between sp^2 hybridised carbon atoms.‡

We thank Dr. E. E. Glover for gifts of material and Dr. J. D. Lee for permission to use his LUX suite of X-ray analysis programs.

(*Received, 5th April* 1978; *Com.* 363.)

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

[1] P. Pauling and T. J. Petcher, *Chem.-Biol. Interactions*, 1973, **6**, 351, particularly p. 361.
[2] D. J. Pointer, J. B. Wilford, and D. C. Bishop, *Nature*, 1972, **239**, 332.
[3] D. J. Pointer and J. B. Wilford, *J.C.S. Perkin II*, 1972, 2259.
[4] E. E. Glover, K. D. Vaughan, and D. C. Bishop, *J.C.S. Perkin I*, 1973, 2595.
[5] L. Bolger, R. T. Brittain, D. Jack, M. R. Jackson, A. E. Martin, J. Mills, D. Poynter, and M. B. Tyers, *Nature*, 1972, **238**, 354.
[6] R. T. Brittain and M. B. Tyers, *Brit. J. Anaesth.*, 1973, **45**(8), 837.
[7] Personal communication published by courtesy of Allen and Hanburys Research Ltd., Priory Street, Ware, Hertfordshire SG12 0DJ.
[8] J. D. Lee, Loughborough University X-ray system, LUX suite of computer programs; J. D. Lee and G. W. Goodacre, *Acta Cryst.*, 1971, **B27**, 1055.
[9] P. Marsau, *Acta. Cryst.*, 1977, **B33**, 2897.