X-Ray Structure Determination of 3,6-*p*-Anisylidenedithio-3-ethyl-*NN'*-dimethylpiperazine-2,5-dione

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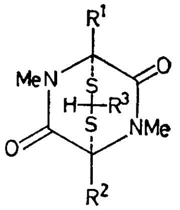
Summary An *X*-ray structure determination of the title compound (**2**), synthesized from the dithioacetal (**1**) by regiospecific metallation with n-butyl-lithium and alkylation with ethyl iodide, was performed; it was shown that the regiospecific metallation is not related to the nature of the substituent at the dithioacetal residue.

IN connection with synthetic studies[1a,b] on natural products of the gliotoxin-sporidesmin class, we observed a regiospecific metallation of the dithioacetal (**1**), and postulated that the regiospecificity could be caused by angle-dependent efficiency of the overlap of the 3*d* orbitals on sulphur with the sp^3 orbital at the bridgehead carbon.[1a] Although it was possible to determine the metallated position in a special case by chemical methods,[1a] a conclusive structure determination, particularly including conformational information, was required for a consideration of the reasons for the regiospecificity. We now report the *X*-ray structure determination of the monoethyl dithioacetal (**2**).



(**1**); $R^1 = R^2 = H$, $R^3 = p\text{-MeOC}_6H_4$
(**2**); $R^1 = Et$, $R^2 = H$, $R^3 = p\text{-MeOC}_6H_4$
(**3**); $R^1 = R^2 = H$, $R^3 = Ph$
(**4**); $R^1 = R^2 = H$, $R^3 = Me$

Compound (**2**) [$\delta(CDCl_3)$ 1·00 (3H, t, *J* 7·5 Hz), 1·95 (1H, m), 2·54 (1H, m), 3·07 (3H, s), 3·20 (3H, s), 3·80 (3H, s), 5·05

(1H, s), 5·14 (1H, s), 6·87, and 7·34 (2H+2H, AB, J 9 Hz)] was synthesized from (**1**) in 60% yield by the method reported previously.[1a] Recrystallization from methanol afforded needles, m.p. 202—203°. *Crystal data:* $C_{16}H_{20}N_2O_3S_2$, monoclinic; $a = 7{\cdot}092(1)$, $b = 16.927(2)$, $c = 15{\cdot}141(2)$ Å, $\beta = 110{\cdot}80(2)°$, $D_m = 1{\cdot}38$ g cm^{-3}, $Z = 4$, space group $P2_1/c$. The structure was determined with Cu-K_α scintillation counter data by symbolic addition methods, and refined by block-diagonal least-squares techniques. The final R value was 0·066 for 2343 observed reflections. Anisotropic thermal parameters were assumed for all the non-hydrogen atoms in the final refinement. 17 hydrogen atoms, which were clearly visible at $R = 0{\cdot}092$, were refined using positional and thermal parameters; the positions of the remaining atoms which were determined from a difference Fourier were not refined and thermal parameters were made identical to those of the carbon atoms to which they were attached. The structure of the dithioacetal (**2**) is shown in the Figure. The present structure is consistent with the one concluded by chemical methods.[1a]

The regiospecificity of metallation is not related to the nature of the substituent at the dithioacetal residue, because parallel results to those with (**1**) were observed with the benzylidenedithioacetal (**3**), m.p. 272—273°, and the ethylidenedithioacetal (**4**), m.p. 186—188°. The bridgehead protons appear in the n.m.r. spectrum at δ 4·88 and 5·03 for (**1**), δ 4·89 and 5·05 for (**3**), and δ 4·83 and 5·00 for (**4**); in all the cases the bridgehead position bearing the proton with the higher chemical shift is that which is metallated.

The present X-ray results show that the dihedral angle C(8)–S(9)–C(6)–H (154°) is close to that for C(8)–S(7)–C(3)–Et (155·7°) and therefore it would be difficult to attribute the regiospecificity to the difference of the efficiency of the overlap of the 3*d* orbitals on sulphur and the sp^3 orbital on the bridgehead positions. An alternative explanation is that the regiospecificity could arise from the different environments around the lone pairs on sulphur atoms [one of the sulphur lone pairs is oriented antiperiplanar to the N(1)–C(6) bond but not to the C(5)–C(6) bond on the same side, while another sulphur lone pair is oriented antiperiplanar to the C(2)–C(3) bond but not to the C(3)–N(4) bond on the other side.[2]]

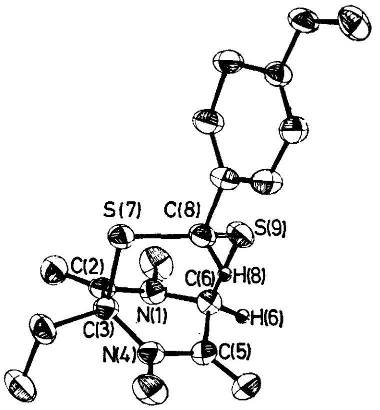


FIGURE. A perspective drawing of the dithioacetal (**2**).

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[1] (a) Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.*, 1973, **95**, 6490; (b) *ibid.*, p. 6492; Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, *ibid.*, p. 6493; S. Nakatsuka, T. Fukuyama, and Y. Kishi, *Tetrahedron Letters.*, 1974, 1549.

[2] The importance of antiperiplanar orientation of the lone pair on oxygen in ozonolysis of acetals and in hydrolysis of amides or esters has been recognized recently; P. Deslongchamps, P. Atlani, D. Frihel, A. Malaval, and C. Moreau, *Canad. J. Chem.*, 1974, **52**, 3651; 1973, **51**, 1665; 1972, **50**, 3405; J. M. Lehn and G. Wipff, *J. Amer. Chem. Soc.*, 1974, **96**, 4048.