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PARTIAL SYNTHESIS OF GLIOTOXIN G, AN EPITETRATHIODIOXOPIPERAZINE

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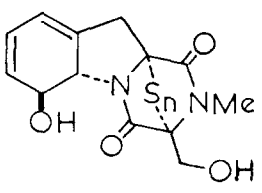
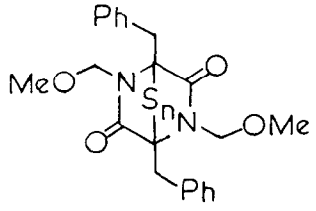
Summary: Gliotoxin (1a) reacted with elemental sulphur, in carbon disulphide containing a catalytic amount of thiolate, to give the corresponding epitetrasulphide, gliotoxin G (1c), recently identified[1] as a minor metabolite of Aspergillus fumigatus.



(1)



(2)

a ; n = 2
b ; n = 3
c ; n = 4

Gliotoxin G (1c) has recently been identified[1] as a new, minor metabolite of Aspergillus fumigatus having immunosuppressive activity. Since the quantities obtained were small (ca. 1 mg) we devised a simple preparation[2] from the readily available epidisulphide, gliotoxin (1a). In a preliminary study, the synthetic, racemic epidisulphide (2a)[3] was treated at ambient temperature with sulphur (2 atom equiv.) in carbon disulphide containing a catalytic amount of lithium hexanethiolate. The reaction was monitored directly by ^{1}H n.m.r. spectroscopy; after 24 h almost complete conversion of (2a) into (2c) had occurred but no signals attributable to the epitrisulphide (2b) were observed at intermediate times. Moreover, higher polysulphides were not observed when an excess of sulphur was used. Similarly, a suspension of gliotoxin (1a) (98 mg, 0.3 mmol) in carbon disulphide (7.5 ml) containing an excess of rhombic sulphur (960 mg) (recrystallised from toluene), to which had been added lithium phenylmethanethiolate (0.03 mmol) (prepared from $PhCH_2SH$ and Bu^nLi in tetrahydrofuran), was stirred at room temperature. The gliotoxin dissolved as the reaction proceeded. After 17 h the mixture was poured onto a silica (t.l.c. grade) column and the excess of sulphur was

eluted with dichloromethane. Elution with ether gave successively gliotoxin (1a), a fraction believed to contain the epitrisulphide (1b)[4], and gliotoxin G (1c). After further purification by t.l.c. [silica plates developed with CH_2Cl_2-EtOAc (2:1)], (1a), (1b), and (1c) were obtained in yields of 13, 26, and 60%, respectively. Gliotoxin G (1c) gave microanalytical data[5] confirming the tetrasulphide structure (1c). The spectroscopic data[5] agreed well with those reported[1] for the natural product.

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References and Notes

1. P. Waring, R.D. Eichner, U.T. Palni, and A. Mullbacher, Tetrahedron Lett., 1986, 27, 735.
2. Cf. S. Safe and A. Taylor, J. Chem. Soc. (C), 1970, 432; dehydrogliotoxin was converted into the corresponding epitrisulphide and epitetrasulphide by heating with dihydrogen disulphide.
3. G.W. Kirby, D.J. Robins, and W.M. Stark, J. Chem. Soc., Chem. Commun., 1983, 812.
4. This material did not crystallise. The chemical ionisation spectrum (reagent gas, isobutane) gave a peak, m/z 359.0210 ($C_{13}H_{15}N_2O_4S_3$ requires M+1, 359.0194) more intense than that for (1c) (see note 5).
5. Gliotoxin G (1c), m.p. 163-164 °C (from acetone) (Found: C, 39.8; H, 3.4; N, 7.0; S, 33.15. $C_{13}H_{14}N_2O_4S_4$ requires C, 40.0; H, 3.6; N, 7.2; S, 32.8%); $[\alpha]_{589}$ -499° and $[\alpha]_{546}$ -607° (c 1.25 in $CHCl_3$); $\nu_{max.}$ (KBr) 3 425, 1 677, and 1 652 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 3.05 and 3.26 (ABq, J 16 Hz, CH_2), 3.12 (s, NMe), 4.00 (s, OH), 4.06 and 4.39 (ABq, J 12 Hz, after D_2O exch., CH_2O), 4.78 and 5.50 (ABq, J 13 Hz, 2 x allylic CH), 5.90 (s, OH), and 5.64-6.04 (m, 3 x vinylic H); m/z (CI; isobutane) 391 (M + 1), 359 (M + 1 - S), 327 (M + 1 - S_2), 263 (M + 1 - S_4), 245 (M + 1 - S_4 - H_2O), 227 (M + 1 - S_4 - 2 H_2O), and 215 (M - S_4 - H_2O - CH_2OH).

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