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THE STEREOCHEMISTRY OF MYXOTHIAZOL

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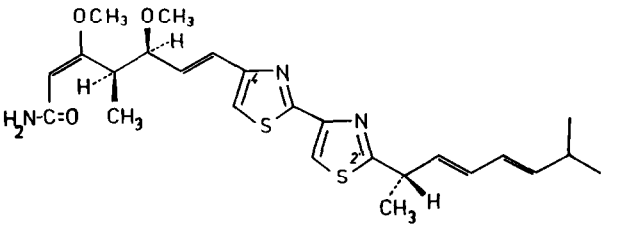
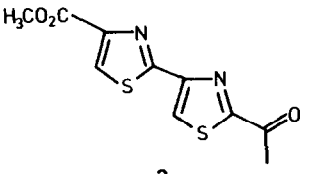
Summary: The absolute configuration of myxothiazol is established as 4(6-carbamoyl-3S,5-dimethoxy-4R-methylhexa-1E,5E-dienyl)-2'-(1S,6-dimethylhepta-2E,4E-dienyl)-2,4'-bithiazole by a combination of chemical methods and X-ray analysis

Recently we have reported on the structure elucidation of myxothiazol (1), an antifungal antibiotic[1,2] from a gliding bacteria, and an inhibitor of the ubiquinol: cytochrom c reductase system[3].



1

Here we present the establishment of the absolute configuration of myxothiazol. Ozone-degradation of myxothiazol followed by an oxidative work-up procedure yielded the acetyl-bithiazole derivative 2 which has been described previously[2].



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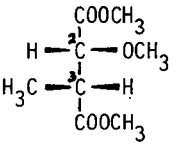
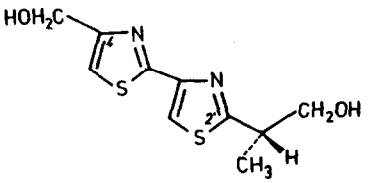


(+)-3

In order to determine the absolute configuration of 3, we synthesised (+)-3 starting from an authentic sample, (2R,3R)-threo-ß-methylmalic acid[8] (α_D=-5.2°,H_2O) by esterification with diazomethane followed by reaction with methyl iodide/ silver oxide. After distillation (120°C/12 mm) the product was purified by preparative glc (OV-17,2m,110°C). 3 displayed a purity of about 99 %(by capillary gc) and gave an α_D-value of + 30°. Since the ozonolysis product 3 of myxothiazol had an α_D-value of + 35° its 2R,3R-configuration is established, resulting in a 3S,4R-configuration for myxothiazol.

In order to examine the third asymmetric centre of myxothiazol, we applied the reductive work-up procedure after ozonolysis. Treatment with sodium borohydride in methanol at -70°C followed by chromatography on silica gel with dichloromethane/methanol (7:1) yielded the expected bithiazol-diol 7 which crystallises from dichloromethane/petrol ether, m.p. 93°C, λ_{max}= 296 nm (logε = 4.01, methanol).



7

Remarkably, 7 shows different α_D-values in chloroform (α_D=+5.4°) and in methanol (α_D= - 8.2°). The high resolution mass spectrum gave M^+= 256.0336 (calculated for $C_{10}H_{12}N_2O_2S_2$: 256.0340). In the proton nmr spectrum(100 MHz) we observe signals at: 7.88(s,5'-H), 7.20(s,5-H), 4.81(AB-system,4'-CH_2-), 3.91 (m,2'-C-CH_2-), 3.40(m,2'-CH-), 1.44 ppm(d,2'-C-CH_3)

The carbon-13 spectrum of 7 shows signals ($CDCl_3$/TMS) at: 175.3 (C-2'), 163.0(C-2), 159.2(C-4), 149.2(C-4'), 115.3 and 114.8(C-5 or C-5'), 66.9(4-CH_2-), 61.2(2'-C-$\underline{C}H_2$-), 41.5 (2'-CH-), and 17.4 ppm (2'-C-$\underline{C}H_3$).

The absolute configuration of 7 was established by X-ray structural analysis as S. 7 crystallises in the monoclinic space group P 2_1 with a= 23.078(4), b= 4.754(1), c= 10.898(4) Å, ß= 100.18(2), Z=4, D_c= 1.45g cm^{-3}. The structure was solved by Patterson and difference syntheses and refined to R= 0.083, R_w= 0.082 for 1761 absorption corrected independent reflections (Cu Kα, $2\theta \leq 115°$, $F^2 \geq 2.5\sigma(F^2)$, μ(Cu Kα)= 38.5 cm^{-1}). There are two independent molecules of 7 in the unit cell, both of which display the same absolute configuration. Solution and refinement of the structure were complicated by the fact that the atom positions of the bithiazole chromophore in the independent molecules are related by a pseudo-centre of symmetry.

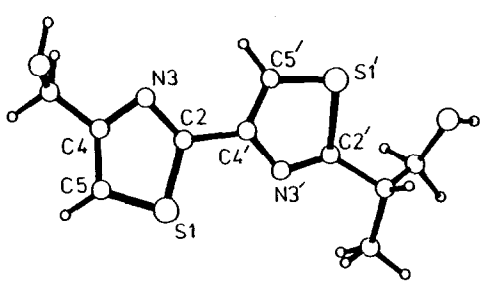


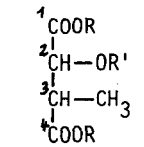
Fig.1. The molecular structure of (S)-7

In addition to 2, we isolated the dimethyl 2-methoxy-3-methylsuccinate (3), (α_D= +35°,Et_2O), after esterification with diazomethane. By a known synthesis of 3[4] we demonstrated the relative configuration of 3 to be threo (t). The proton nmr spectra of compounds in this series provided a well suited tool for the establishment of relative configurations. In particular,the chemical shift of the 2-H protons may serve as a probe for the determination of the relative configurations. In 3 (threo) this signal appears at 4.19 ppm ($CDCl_3$), in the erythro analog of 3 (3 e) at 3.95 ppm. Because of its relevance for further studies on the stereochemistry in this series of compounds[5], we have tabulated all the ^1H and ^{13}C nmr data of the synthesised compounds (Tables 1 and 2). The threo-dimethyl ester 5 (5 t) and the erythro ester 6 (6 e) have been already described by Mori et al.[6,7] who also established their absolute configurations.

Tab.1. ^1H nmr data of erythro (e) and threo (t) 3-6 ($CDCl_3$/TMS except 4 e,t: acetone-d_6)

		2-H	2-OMe	3-H	3-CH_3	1,4-Me ester		1,4-OCH_2-	1,4-OCH_2-CH_3
3	e	3.95 d, J=6.8	3.42 s	2.97 dq	1.19 d, J=7.2	3.78 s	3.71 s	-	-
	t	4.19 d, J=4.7	3.44 s	2.94 dq	1.16 d, J=7.2	3.78 s	3.72 s		
4	e	4.33 d, J=4.8[1]	-	2.98 dq	1.26 d, J=7.2	-	-	-	-
	t	4.66 d, J=4.2[1]	-	2.95 dq	1.13 d, J=7.2	-	-	-	-
5	e	4.42 d, J=5.8[1]	-	2.97 dq	1.21 d, J=7.2	3.80 s	3.70 s	-	-
	t	4.63 d, J=4.2[1]	-	2.95 dq	1.17 d, J=7.2	3.82 s	3.74 s	-	-
6	e	4.25 d, J=3.8[1]	-	3.02 dq	1.29 d, J=7.3	-	-	4.26 m 4.14 m	1.30 t 1.25 t
	t	4.60 d, J=3.5[1]	-	2.93 dq	1.17 d, J=7.3	-	-	4.28 m 4.19 m	1.31 t 1.28 t

footnotes: 1) After deuterium exchange.



3 e,t R=R'=CH_3

4 e,t R=R'= H

5 e,t R=CH_3,R'=H

6 e,t R=C_2H_5,R'=H

Tab.2. ^{13}C nmr data of threo (t) and erythro (e) 4 and 6 (in acetone-d_6/TMS)

		C-2	C-3	3-CH_3	C-1, C-4	1,4-OCH_2-	1,4-OCH_2-CH_3
4	e	72.9	43.7	13.3	175.0 174.6	- -	- -
	t	71.9	43.2	10.56	175.4 174.8	- -	- -
6	e	73.4	44.3	13.06	173.4 173.2	61.6 60.9	14.4 14.4
	t	72.5	43.9	11.2	173.1 173.2	61.7 60.9	14.4 14.4

It was, therefore, necessary to tie the bond lengths in the independent molecules to one another (± 0.02 Å) and these were introduced as parameters in the least - squares refinement. The C-2' side chain of the first molecule is disordered. The absolute configuration was determined by a Hamilton R-test[9] on the generalised reliability indices R_G for a final refinement (without weights). R_G is 0.08576 for the R-configuration and 0.08530 for the S-configuration, and the ratio of these values allows a highly significant rejection of the R-configuration at the 99.5 % confidence level.

The chromophore of 7 is nearly planar. The thiazole rings are inclined to one another at respective angles of 3.5° and 2.1° in the two independent molecules. The distribution of bond lengths and angles is similar to that found for another bithiazole derivative[10].

From the above investigations[11] follows the stereochemistry of myxothiazol as depicted in formula 1.

References and footnotes

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11) We are grateful to Dr.V.Wray and Dr.L.Grotjahn, both of our institute, for nmr spectra and the high resolution mass spectrum, respectively.

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