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SYNTHESIS OF BOSTRYCOIDIN AND 8-O-METHYLBOSTRYCOIDIN

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Summary. The antibiotic bostrycoidin (1) and its 8-O-methyl derivative (2), the only natural 2-azaanthraquinones, have been synthesized for the first time.

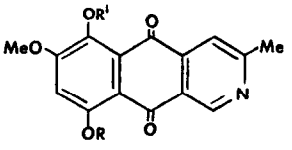
This communication reports the synthesis of the mould metabolites bostrycoidin (1) and 8-O-methylbostrycoidin (2), the only natural 2-azaanthraquinones. Bostrycoidin is elaborated by Fusarium bostrycoides[1] and F. solani[2] and its 8-O-methyl derivative by F. moniliforme[3]. The former compound strongly inhibits growth of the tubercle bacillus in vitro.

Synthesis of (1) and (2) was planned from the azanaphthoquinone (3) itself readily available from 3-methylisoquinoline[4]. Annelation of (3) was explored using 1,1-dimethoxyethene under conditions where carbocyclic naphthoquinones undergo 1:2-addition of this reagent to give anthraquinones[5]. Reaction of (3) was found to give a mixture (7:1) of the 2-azaanthraquinones (4) and (5) respectively in 70% overall yield. This regioselectivity would be consistent with addition being controlled by the more electron deficient carbonyl group γ to the pyridine ring[6]. However, in order to confirm this expectation it was necessary to develop an independent procedure, since the spectral properties of the isomers (4) and (5) were almost identical.

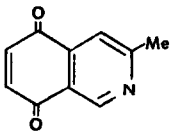
A confirmatory approach to (5) was based on the work of Minisci and coworkers[7]. Reaction of the benzoyl radical derived from 3,5-dimethoxybenzaldehyde with 6-methylpyridine-3-carbonitrile[8] gave a mixture of the γ- and α- acylated pyridines(6) (13%) and (7) (38%). These were readily differentiated on the basis of ^{1}H n.m.r. spectra ($CDCl_3$) the pyridyl protons of the former resonating as singlets [δ 8.92 (H2), 7.35 (H5)] and of the latter as ortho-coupled doublets (J 8Hz) [δ 8.04 (H4), 7.43 (H5)].

Compounds (6) and (7) were converted into azaanthraquinones under remarkably mild conditions. When hydrogen chloride was bubbled through a solution of the former in 1,2-dichloroethane and the product was hydrolysed with aqueous ammonia, compound (5), m.p. 215-215.5°, was obtained in 35% yield, identical with the product from (3). Its n.m.r. spectrum was amenable to first order analysis, containing singlets at δ 9.41 and 7.81, and doublets (J 2.5Hz) at 7.43 and 6.84. Similar ring closure of (7) gave the 1-azaanthraquinone (8) m.p. 240-243° (dec.), δ 8.49 and 7.55, doublets (J 8Hz), and 7.54 and 6.82 doublets (J 2.5Hz).

When a solution of (5) in aqueous acetonitrile containing acetic acid was irradiated with a 400W medium pressure mercury lamp 6,8-dimethoxy-5-hydroxy-3-methyl-2-azaanthraquinone (2) was obtained (74%). It was identical in all respects with natural 8-O-methylbostrycoidin. Selective demethylation of this product with boron trichloride gave 5,8-dihydroxy-6-methoxy-3-methyl-2-azaanthraquinone (1) (100%) similarly identical with bostrycoidin. This not only



	R	R'
1	H	H
2	Me	H
9	Me	Me



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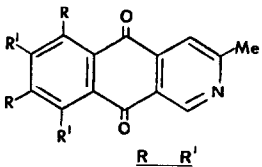
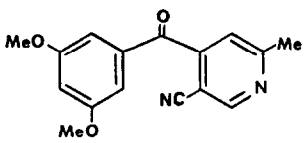


	R	R'
4	OMe	H
5	H	OMe



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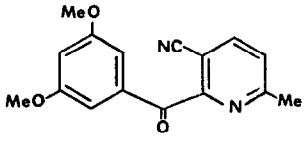

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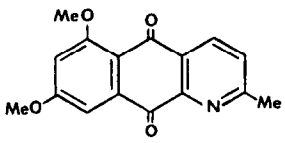

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serves as a total synthesis of the antibiotic but also confirms placement of the β-methoxy group at C-6, an assignment previously based on biogenetic analogy[2].

When solutions of (5) in methanol were exposed to bright sunlight the trimethyl ether (9) was obtained and this was converted to bostrycoidin by selective demethylation using boron trichloride. Similarly 1,3-dimethoxyanthraquinone has been found to undergo photo-hydroxylation or -methoxylation in the 4-position[9]. The generality of these processes is being investigated.

Satisfactory elemental analyses and spectra have been obtained for all new compounds reported in this work. We are grateful to Dr G. P. Arsenault and Dr P. S. Steyn for gifts of bostrycoidin and 8-O-methylbostrycoidin respectively and acknowledge an Australian Post-graduate Research Award (to K.R.D.).

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