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A STRUCTURAL REVISION OF PICRONOCCELLIN

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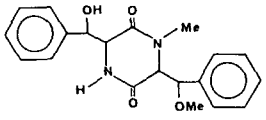
Abstract: The structure of picroroccellin has been revised to (2).

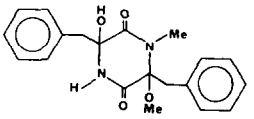
Picroroccellin, a bitter substance first extracted from the lichen Roccella fuciformis DC. in 1877[1] has not been found since that date despite a recent systematic search by Huneck.[2]

Forster and Saville[3] subsequently proposed structure (1) for picroroccellin but on critical re-examination[4] of their results we have deduced that picroroccellin could equally well be formulated as (2).



Substitution on nitrogens may be reversed.

(1)



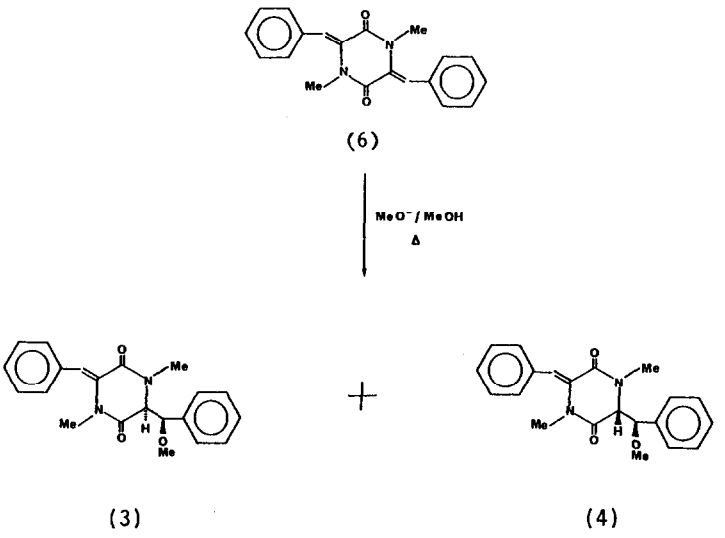
Substitution on nitrogens may be reversed.

(2)

As no natural material was available for conventional structural analysis, we resorted to the synthesis of several derivatives of picroroccellin. Initial goals were the three possible formultions for methylanhydropicroroccellin, (3),(4), and (5).

The Michael addition of methoxide ion to methylxanthoroccellin (6) gave a mixture of the required β-methoxy-2,5-piperazinediones (3) and (4) in ca. 40% combined yield. Subsequent fractional recrystallization from ethyl acetate/light petroleum gave the erythro-isomer (4) (21%) and the threo-isomer (3) (13%).

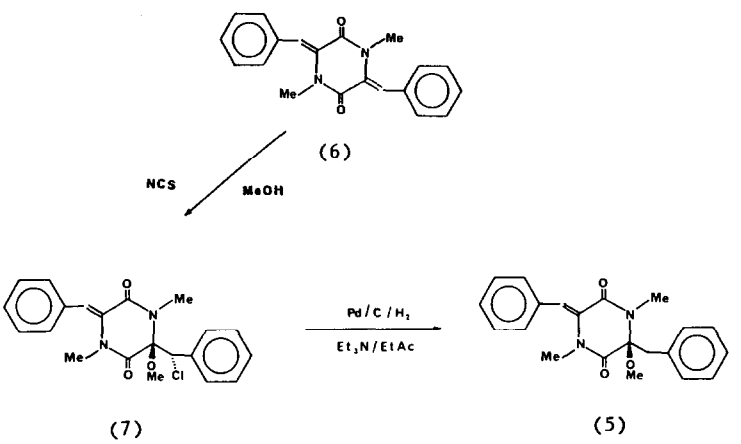
Slow recrystallization of each diastereomer resulted in the formation of racemic mixtures although individual crystals of each diastereomer were shown to be optically active by ORD. This spontaneous resolution allowed the direct comparison of m.p.'s of these two diastereomers ((3) and (4)) and material derived from the natural product. Both of the β-methoxy-2,5-piperazinediones (3) and (4) had higher m.p.'s (7° and 16° respectively) than naturally derived methylanhydropicroroccellin.



(6)

(3) (4)

Treatment of methylxanthoroccellin (6) with N-chlorosuccinimide (NCS) in methanol gave the 3-(chlorophenylmethyl)-3-methoxy-2,5-piperazinedione (7). Hydrogenolysis of the carbon-chlorine bond using pallidized charcoal gave the desired 3-methoxy-2,5-piperazinedione (5) in good yield.



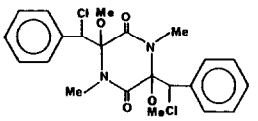
(6)

(7) (5)

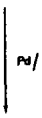
Compound (5) had a m.p. 40° above that reported for naturally derived (optically active) methylanhydropicroroccellin. Subsequent X-ray analysis established that the synthetic material was a racemic compound, so it is possible that (5) might still be the correct structure for methylanhydropicroroccellin.

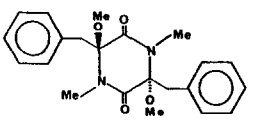
With the limited data available for picroroccellin and its derivatives, we anticipated that a comparison of the reactivities of (3), (4) and (5) could provide additional evidence for the structure of the natural product. Thus treatment of (3) or (4) with a catalytic amount of hydrochloric acid in refluxing acetic acid resulted in almost quantitative recovery of these compounds. In contrast the 3-methoxy-2,5-piperazinedione (5) gave methylxanthoroccellin (6) after only 15 minutes at reflux with these reagents. Furthermore, the 3-methoxy-2,5-piperazinedione (5) was thermally stable at 180°, but at 220°, (5) eliminated methanol to give methylxanthoroccellin (6). In contrast the β-methoxy-2,5-piperazinediones (3) and (4) were stable at these temperatures. The reactions of the 3-methoxy-2,5-piperazinedione (5) entirely parallels that reported for picroroccellin[3] and this is consistent with the oxygen functions being located at the 3,6 positions of the 2,5-piperazinedione ring.

Subsequently, we embarked on the synthesis of dimethylpicroroccellin since the reported lack of optical activity of the naturally derived material was only consistent with the trans-structure (8). Treatment of methylxanthoroccellin (6) with NCS (2 eq.) in methanol gave (9) as a mixture of diastereomers. Hydrogenolysis of the carbon-chlorine bonds gave a mixture of (8) and the cis-isomer (10). The major product (10) (ca. 95%) was converted cleanly to the desired trans-isomer (8) by refluxing the crude reaction mixture in methanol containing a catalytic amount of hydrochloric acid. The two diastereomers were readily distinguishable by their ^{1}H n.m.r. spectra. Isomer (8) displayed an O-methyl singlet at δ 1.9 while (10) displayed this same resonance at δ 3.1.

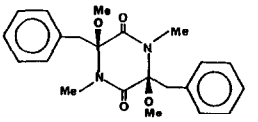


(9)





(8)



(10)

These differences in chemical shifts arise from the shielding of protons cis-disposed to the aromatic side chain. The m.p. (229 - 230°) and physical properties of the pure trans-isomer (8) were identical with those reported for dimethylpicroroccellin.[3]

In conclusion we have established that the structure of picroroccellin should be revised to (2) and that dimethylpicroroccellin has the trans-geometry depicted in (8).

REFERENCES

1) Stenhouse, J., and Groves, C., Annalen, 1877, 185, 14.
2) Huneck, S., Forschr. Chem. Org. Naturstoffe, 1971, 29, 216.
3) Forster, M.O., and Saville, W.B., J. Chem. Soc., 1922, 816.
4) Marcuccio, S.M., Ph.D. Thesis. (ANU 1982).

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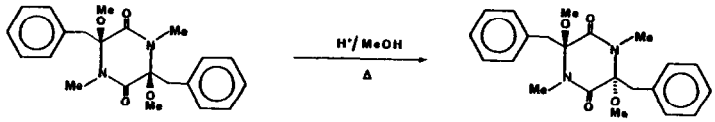

(10) (8)

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