THE SYNTHESIS OF CRYPTOPLEUROSPERMINE, A BENZILIC ALKALOID OF CRYPTOCARYA PLEUROSPERMA

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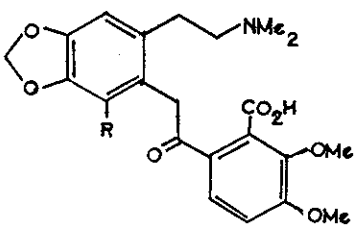
Cryptopleurospermine 5 is synthesised from the aldehydes 13 and 15 through the intermediacy of the trimethylsilyl cyanohydrin of 13 used as a carbonyl anion equivalent.

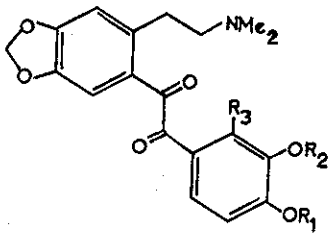
In recent years a small group of benzylisoquinoline alkaloids, bearing a dimethylaminoethyl side chain derived from *in vivo* oxidative degradation of the nitrogen-containing ring, have been isolated. In this aspect of their structure they resemble the well-known opium alkaloid narceine 1 and the more recent[1] hydrasteine 2 and their corresponding imides[2]. These imides however, as well as the imides of the analogous bicuculleine[2,3] (also known as fumaramine), are likely to be artifacts formed in the isolation process. Other members of the group differ in the oxidation states of the two central benzylic carbon atoms. Bicucullinine 3 (isolated from *Corydalis ochroleuca*), N-methyloxohydrasteine 4 (from *Fumaria officinalis*[1]) and cryptopleurospermine 5 (from *Cryptocarya pleurosperma*[4]) are all benzils whereas peshawarine[5] 6 is a considerably reduced analogue of bicucullinine. Among all these

alkaloids, cryptopleurospermine alone does not possess a carboxyl group



1 R = OMe

2 R = H

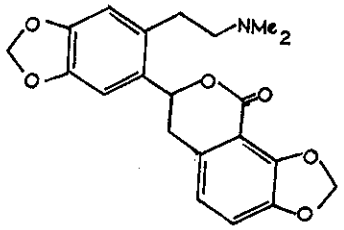


3 R_1 + R_2 = CH_2, R_3 = CO_2H

4 R_1 = R_2 = Me , R_3 = CO_2H

5 R_1 = Me , R_2 = R_3 = H

18 R_1 = Me , R_2 = CH_2OMe, R_3 = H



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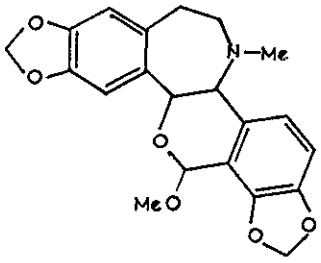

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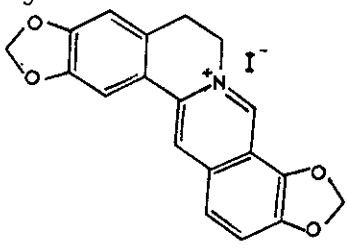

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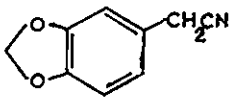
on the 'lower' benzene ring. Some of the alkaloids of the group have been synthesised from known natural phthalideisoquinolines[1] while peshawarine has been prepared from coptisine iodide 7[6] and from rhoeadine 8[7]. Bicucullinine and cryptopleurospermine have not been synthesised.

We now report a simple synthesis of cryptopleurospermine by a route that can be adapted to the synthesis of bicucullinine and peshawarine as well. 3,4-Methylenedioxyphenylacetonitile 9, prepared from piperonal

in the usual way[8] was hydrogenated in ethyl formate and ethanol saturated with ammonia at 900 p.s.i. with a Raney Nickel catalyst to yield the formamide 10 (80%) which was N-methylated (methyl iodide sodium hydride dimethylformamide) and reduced (lithium aluminum hydride tetrahydrofuran) to NN-dimethyl homopiperonylamine 11 (75% overall). This was brominated (bromine glacial acetic acid) and the resulting bromide 12 (85%) was treated successively with n-butylithium in THF and dimethylformamide to yield the aldehyde 13 (80%) identical in its properties with a degradation product[4] of cryptopleurospermine.



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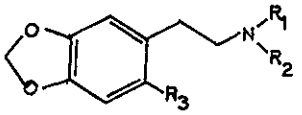
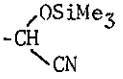


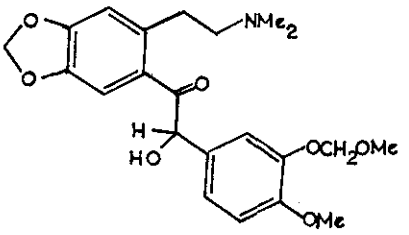
10 R_1 = CHO, R_2 = R_3 = H

11 R_1 = R_2 = Me, R_3 = H

12 R_1 = R_2 = Me, R_3 = Br

13 R_1 = R_2 = Me, R_3 = CHO

14 R_1 = R_2 = Me, R_3 = 



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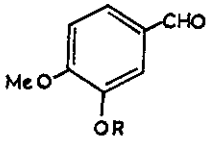

15 R = CH_2O Me

16 R = H

The aldehyde 13 upon treatment with cyanotrimethylsilane[9] gave the trisilylmethylcyanohydrin 14 as a distillable oil [84%, b.p. 126-130 (0.02 Torr); n.m.r. (δ) : 7.05 (s, 1H); 6.71 (s, 1H); 5.96 (s, 2H); 5.66 (s, 1H); 2.4-3.0 (m, 4H); 2.33, (s, 6H); 0.23 (s, 9H)].

Deprotonation of 14 with lithiumdiisopropylamide in dimethoxyethane[10] under nitrogen followed by treatment with O-methoxymethylisovanillin 15[11] yielded a product which after mild acid hydrolysis and work-up appeared to be (n.m.r.) a mixture of benzoin 17 and benzil 18. This mixture was therefore left exposed to air in methylene chloride at room temperature for a further 48 hours to provide the benzil 18 [n.m.r. (δ) 7.82 (d, 1H, J_{meta}= 1.5 Hz), 7.60 (q, 1H, J_{meta}= 1.5 Hz, J_{ortho}= 9 Hz), 7.10 (s, 1H), 6.95 (d, 1H, J_{ortho} = 9 Hz), 6.87 (s, 1H) 6.03 (s, 2H); 5.30 (s, 2H); 3.97 (s, 3H); 3.53 (s, 3H); 3.22 (m, 2H), 2.60 (m, 2H); 2.35 (s, 6H); i.r. 1670, 1600 cm^{-1}].

The methoxymethyl group was removed by brief refluxing with hydrogen chloride in methanol and the product crystallised from acetone to yield cryptopleurospermine 5 identical in its physical properties with those reported[4] for the natural alkaloid.

Acknowledgement

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