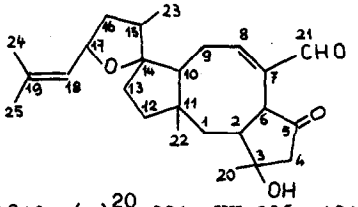
Tetrahedron Letters No.11, pp. 1211-1218, 1966. Pergamon Press Ltd.
Printed in Great Britain.

THE CONSTITUTION OF COCHLIOBOLIN

L. Canonica, A. Fiecchi, M. Galli Kienle, A. Scala
Istituto di Chimica Organica dell'Università
Centro Naz. Chim. Sost. Org. Nat. del C.N.R. - Milano (Italy)

(Received 17 December 1965; in revised form 21 January 1966)

We propose the formula 1 for the cochliobolin,[1] $C_{25}H_{36}O_4$ (MS 400),[a] a metabolic product of Helminthosporium orizae:



1

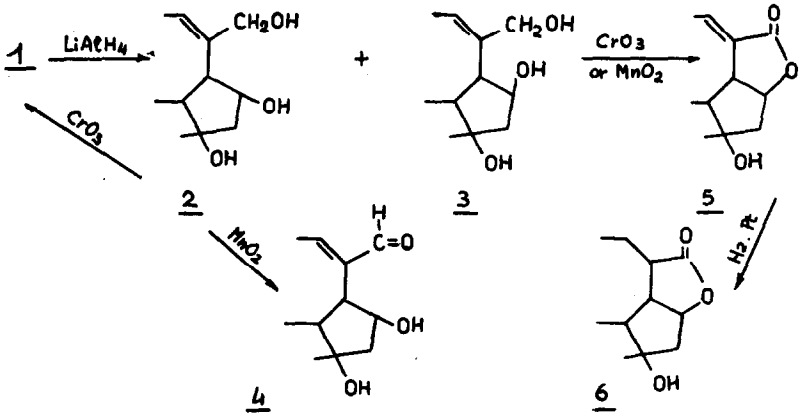
1 has m.p. 181°; $(\alpha)_D^{20}$ 301; UV 236, 10100; IR ($CHCl_3$) 3450, 2730, 1742, 1673, 1635; its NMR spectrum shows signals at 0.83 s C11-CH_3, 1.12 d(7) (DR 2.28 s), C15-CH_3, 1.37 s C3-CH_3, 1.78 broad s (DR 5.18 s) two C19-CH_3, 2.65 AB q(20) C4-H_2, 3.25 d(10) (DR 2.28 s) OH C6-H, 4.45 m (DR 1.75 d, 5.18 t) C17-H, 5.18 broad d(7) (DR 1.78 d, 4.45 s) C18-H, 7.21 t (DR 2.22 s) C8-H, 9.23 s C21-H. 1 yields a monoepoxide and an anhydrobis-2,4-dinitrophenylhydrazone m.p. 252°; in fact 1 is dehydrated in acid and alkaline medium to 3-anhydrocochlio-

a) MS indicates the determination of the molecular weight by mass spectrometry; $(\alpha)_D$ were determined in chloroform; UV spectra were run in methanol (λ_{max} in $m\mu$, intensities as ε); IR spectra in nujol and ν_{max} in cm^{-1}; NMR spectra were determined in $CDCl_3$ (at 60 Mc, TMS as internal reference), chemical shifts as δ=ppm (J in cps); DR signifies a double resonance spectrum at the indicated frequency.

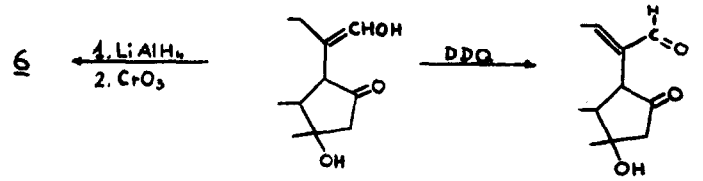
bolin, $C_{25}H_{34}O_3$; MS 382; m.p. 135°; $(\alpha)_D^{20}$ 164; UV 232, 20900; IR 2700, 1695, 1675, 1640, 1620; NMR spectrum of the 3-anhydro derivative shows disappearance of the signals at 1.37, 2.65, 3.25, present in 1, while new signals at 2.09 broad s C3-CH_3, 3.47 d(5) C6-H, 6.11 s C4-H are observed.

With $LiAlH_4$ 1 yields two stereoisomeric triols $C_{25}H_{40}O_4$, 2 and 3: 2 (MS 404); m.p. 158-60° (uncrystallizable dibenzoate) and 3 (MS 404); m.p. 176-78° (dibenzoate m.p. 148-51°).

2 yields 1 with CrO_3 in pyridine and 4 with MnO_2. 4 $C_{25}H_{38}O_4$ shows UV 240, 8000; IR 3500, 3350, 1675, 1630. 3 with CrO_3 in pyridine or with MnO_2 yields 5 $C_{25}H_{36}O_4$; MS 400; m.p. 182-4°; UV 227, 10050; IR ($CHCl_3$) 3700, 3500, 1750, 1685; NMR spectrum of 5 shows disappearance of the signals at 1.37, 1.78, 2.65, 3.25, 7.21, 9.23 present in 1 while new signals at 1.25 s C3-CH_3, 1.5 OH, 1.70 broad s two C19-CH_3, 3.56 m C6-H, 4.9 m C5-H, 7.0 m C8-H are observed. 5 yields 3 with $LiAlH_4$. On hydrogenation 5 yields 6, $C_{25}H_{40}O_4$; MS 404; m.p. 126°; IR 3510, 1740; NMR spectrum of 6 shows disappearance of the signals at 1.70, 3.56, 4.45, 4.9, 5.18, 7.0 present in 5 while new signals at 0.89 d(6) two C19-CH_3, 3.8 m C17-H, 5.07 m C5-H are observed. These results are in agreement with the following scheme:



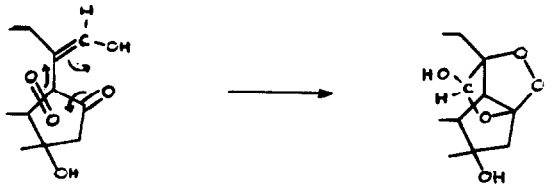
On hydrogenation 1 yields 7, $C_{25}H_{40}O_4$; MS 404; m.p. 156-7°; IR ($CHCl_3$) 3340, 3110, 1740, 1663; NMR spectrum of 7 shows disappearance of the signals at 1.78, 2.65, 3.25, 4.45, 5.18, 7.21, 9.23 present in 1, while new signals at 0.91 d(7) two C19-CH_3, 2.52 s C4-H_2, 2.9 d(10) C6-H, 3.76 m C17-H, 4.8 broad s OH, 6.3 m C21-H, 8.63 m OH are observed. 7 yields a mono-4-nitrobenzoate $C_{32}H_{43}NO_7$; m.p. 132-5° which shows two signals at 3.38 d(7) and 7.18 broad s in its NMR spectrum (respectively at 2.9 and 6.3 in 7). With acids such a derivative yields an isomer m.p. 185-7° which shows two signals at 3.6 d(12) and 7.42 s. Both the 4-nitrobenzoates yield the 3-anhydroderivatives with acids. With $LiAlH_4$ 7 yields two isomeric hemiacetals, which yield 6 with CrO_3 in pyridine. With 2,3-dichloro-5,6-dicyanobenzoquinone 7 yields 8, $C_{25}H_{38}O_4$; the UV spectrum of that is identical to that of 1 and the IR spectrum differs only in the fingerprint region; NMR spectrum of 7 shows disappearance of the signals at 1.78, 4.45, 5.18 present in 1 while new signals at 0.92 d(6) two C19-CH_3 and 3.74 m C17-H are observed. Owing to these reasons we suggest the tentative formula 7. In this particular case the aldehyde group is stabilized in enol form by steric influences; the spectroscopic properties of 7 suggest that the C3-OH is involved in this stabilization through a hydrogen bond.



7 8

With O_2 on Pd-C 7 yields a peroxide having the tentative for-

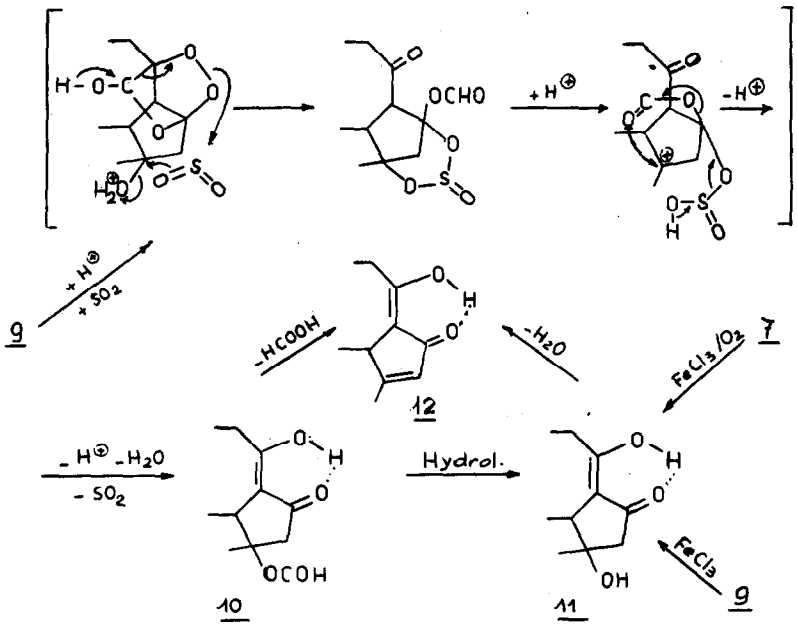
mula 9 $C_{25}H_{40}O_6$ (MS: m/e = 374 = P - 62); m.p. 115°; IR 3500, 3450; NMR spectrum of 9 shows disappearance of the signals at 1.37, 2.52, 2.9, 4.8, 6.3, 8.63 present in 1 and 7 while new signals at 1.24 s C3-CH_3, 3.27 d(5) C6-H, 4.02 d(13.4) C21-OH, 5.06 d(13.4) C21-H, 5.88 OH are observed.



7 9

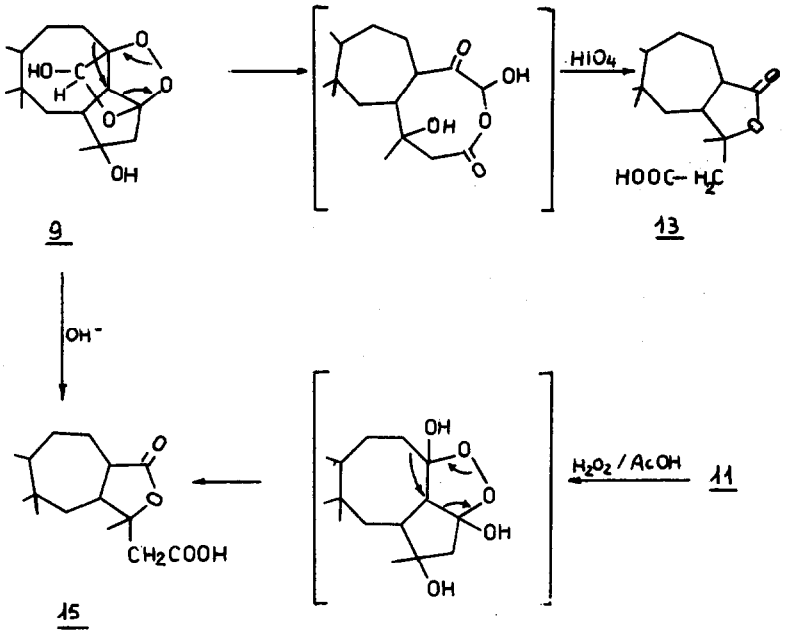
In fact with SO_2 (with neither SO_3^{--} nor HSO_3^-) 9 yields 10 quickly; by-products were observed, but no H_2SO_4 was formed. 10 $C_{25}H_{38}O_5$, has m.p. 120-2°; UV 290, 9600 (in alkali 313, 15500); IR 1720, 1650, 1610, 1190; NMR spectrum of 10 shows signals at 0.83 s C11-CH_3, 0.98 d(7) C15-CH_3 and two C19-CH_3, 1.62 s C3-CH_3, 2.8 s C4-H_2, 3.04 m C2-H, 3.86 m C17-H, 8.05 s C21-H. By saponification, 10 yields formic acid and 11 $C_{24}H_{38}C_4$; MS 390; m.p. 85-96°; UV 290, 9600 (in alkali 313, 17700); IR ($CHCl_3$) 3620, 3430, 1750, 1660, 1610; NMR spectrum of 11 shows disappearance of the signals at 1.62, 2.8, 8.05 present in 10 while signals at 1.38 s C3-CH_3, 2.44 s C4-H_2 are observed. With hydrazine 11 yields a pyrazole $C_{24}H_{38}N_2O_2$; MS 386; m.p. 109-112°; UV 226, 6730 (in acidic medium 233, 8500). By deformylation of 10 or dehydration of 11 we obtain 12 $C_{24}H_{36}O_3$; m.p. 102-4°; UV 245, 8140 - 310, 5500 (in alkaline medium 335, 9350); NMR spectrum of 12 shows disappearance of the signals at 1.62, 2.8, 3.04, 8.05 present in 10 while new signals at 2.09 s C3-CH_3, 3.14 m

C2-H, 6.02 s C4-H are observed. 11 is also obtained from 7 with O_2 and $FeCl_3$ and from 9 with $FeCl_3$. Owing to these results we can explain this reaction as follows:



With one mole of HIO_4 9 yields quantitatively formic acid and a monocarboxylic acid 13 $C_{24}H_{38}O_5$; m.p. 162-5° which yields a methyl ester 14 $C_{25}H_{40}O_5$; MS 420; b.p. 170°/10^{-4}Torr; IR 1760, 1740; NMR spectrum of 14 shows signals at 0.8 s C11-CH_3, 0.88 d(6) two C19-CH_3, 0.99 d(7) C15-CH_3, 1.37 s C3-CH_3, 2.7 s C4-H_2, 2.8 m C2-H and C6-H, 3.68 s CH_3 ester, 3.87 m C17-H. Its mass spectrum shows a peak at m/e = 347 = P - CH_2COOCH_3. From the above data we can explain the reaction with HIO_4 as shown in the scheme at the next page.
In alkaline medium 9 yields the acid 15 $C_{24}H_{38}O_5$; m.p. 214-7°; physical properties of 15 (and of its methyl ester 16 $C_{25}H_{40}O_5$ b.p. 170°/10^{-4}Torr) are very similar to the 13 and 14 ones.

15 is also obtained from 11 with H_2O_2 in acetic acid. We explain the reaction in this manner:

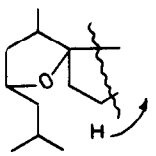


With sodium methoxide in methanol 14 and 16 yield a mixture of two dicarboxylic mono-α,β-insaturated acids $C_{24}H_{38}O_5$; m.p. 80-90°; UV 225, 11700.

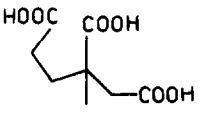
On hydrogenation 3 yields 17 $C_{25}H_{44}O_3$; MS 392; m.p. 160-3°; IR 3570, 3470, 3430; NMR spectrum shows signals at 0.8 d(6) C15-CH_3, 0.87 s C11-CH_3, 0.88 d(6) two C19-CH_3, 1.32 s C3-CH_3, 1.55 3OH, 2.05 s C7-CH_3, 3.18 m C6-H, 4.45 m C5-H, 6.65 m C8-H. Its mass spectrum shows the main peak m/e = 225 = P - C_8H_{17} - $3H_2O$, which suggests the presence of a saturated aliphatic chain C_8H_{17}. All the other derivatives of 1 we investigated by mass spectrometry have no significant peaks at m/e = P - C_8H_{17} - nH_2O, but the most abundant peak is at

m/e = 165 = $C_{11}H_{17}O$ for the derivatives having an isopropylidene group and m/e = 167 = $C_{11}H_{19}O$, 18, for ones having an isopropylic group.

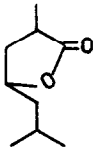
Owing to these results we suggest that on hydrogenation of 3 the ether bridge between C14 and C17 was cleaved the Δ_{18} hydrogenated and the C21-H_2OH group hydrogenolyzed to form a methyl group.



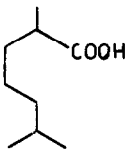
18



19

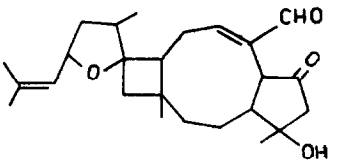


20



21

With perbenzoic acid, acid hydrolysis and HIO_4 1 yields acetone; with HNO_3 1 gives 19 and all its nor-derivatives; 19 can be also obtained from 7 with the lactone 20; 17 yields 19, all its nor-derivatives and 21. 19, 20, 21, show IR, NMR MS spectra identical to synthetized products of unequivocal structure. With HNO_3 7 does not yield acids having a longer chain than 19; this result suggests that in the original structure the quaternary methyl group, appearing in 19, must be separated from the Δ_7 by a trisubstituted carbon atom. Therefore, for cochliobolin the constitutions 1 or 22 are possible only.



22

We propose the formula 1 for cochliobolin since such an ion

as 18, occuring in its mass spectrum, cannot be easily explained according to 22.

Recently Nozoe et al.[2] deduced for ophiobolin the structure 1, including the absolute configuration by X-ray crystallographic analysis of its bromomethoxy derivative 23. We have observed that physical constants of cochliobolin and of its bromomethoxy derivative are very similar with the reported constants of ophiobolin and of its bromomethoxy derivative[2] and we agree with Nozoe et al. in suspecting the identity of cochliobolin with ophiobolin.

Acknowledgement.- We are very grateful to drs. G. Nencini and T. Salvatori of Laboratori Riuniti SNAM for their decisive interpretations of mass spectra.

REFERENCES

1. M. Orsenigo, Phytopatol. Z. 29, 189 (1957)
2. S. Nozoe, M. Morisaki, K. Tsuda, Y. Iitaka, N. Takahashi, S. Tamura, K. Ishibashi, M. Shirasaka, J. Am. Chem. Soc. 87, 4968 (1965)